

NON-STEROIDAL IL-5 INHIBITORS, PROCESSES AND INTERMEDIATES
FOR THEIR PREPARATION AND PHARMACEUTICAL COMPOSITIONS
COMPRISING SAID INHIBITORS.

5 The present invention relates to IL-5 inhibiting 6-azauracil derivatives
useful for treating eosinophil-dependent inflammatory diseases, to processes
and intermediates for their preparation as well as to pharmaceutical
compositions comprising the said derivatives. It further relates to the use of
such derivatives as a medicine, and to processes for marking a receptor or
10 imaging an organ using the said derivatives.

Eosinophil influx, leading to subsequent tissue damage, is an important
pathogenic event in bronchial asthma and allergic diseases. The cytokine
interleukin-5 (IL-5), produced mainly by T lymphocytes as a glycoprotein, induces
15 the differentiation of eosinophils in bone marrow and, primes eosinophils for
activation in peripheral blood and sustains their survival in tissues. As such, IL-5
plays a critical role in the process of eosinophilic inflammation. Hence, the
possibility that inhibitors of IL-5 production would reduce the production,
activation and/or survival of eosinophils provides a therapeutic approach to the
20 treatment of bronchial asthma and allergic diseases such as, atopic dermatitis,
allergic rhinitis, allergic conjunctivitis, and also other eosinophil-dependent
inflammatory diseases.

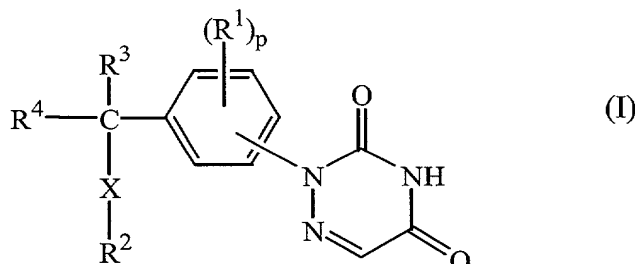
Steroids, which strongly inhibit IL-5 production *in vitro*, have long been used as
the only drugs with remarkable efficacy for bronchial asthma and atopic
25 dermatitis, but they cause various serious adverse reactions such as diabetes,
hypertension and cataracts. Therefore, it would be desirable to find non-
steroidal compounds having the ability to inhibit IL-5 production in human
T-cells and which have little or no adverse reactions.

US 4,631,278 discloses α -aryl-4-(4,5-dihydro-3,5-dioxo-1,2,4-triazin-
30 2(3*H*)-yl)-benzene-acetonitriles and US 4,767,760 discloses 2-(substituted
phenyl)-1,2,4-triazine-3,5(2*H*,4*H*)-diones, all having anti-protozoal activity, in
particular, anti-coccidial activity. EP 831,088 discloses 1,2,4-triazine-3,5-diones

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as anticoccidial agents. WO99/02505 discloses 6-azauracil derivatives which prove to be potent inhibitors of the production of IL-5.

The present invention first relates to compounds having the formula:



the N-oxides, the pharmaceutically acceptable addition salts and the stereochemically isomeric forms thereof, wherein :

p represents an integer being 0, 1, 2, 3 or 4;

X represents O, S, NR⁵ or a direct bond or-X-R² taken together may represent cyano;

Y represents O, S, NR⁵, or S(O)₂;

each R¹ independently represents C(=O)-Z-R¹⁴, C₁₋₆alkyl, halo, polyhaloC₁₋₆alkyl, hydroxy, mercapto, C₁₋₆alkyloxy, C₁₋₆alkylthio, C₁₋₆alkylcarbonyloxy, aryl, cyano, nitro, Het³, R⁶, NR⁷R⁸ or C₁₋₄alkyl substituted with C(=O)-Z-R¹⁴, Het³, R⁶ or NR⁷R⁸;

R² represents Het¹, C₃₋₇cycloalkyl optionally substituted with C(=O)-Z-R¹⁴, C₁₋₆alkyl or C₁₋₆alkyl substituted with one or two substituents selected from C(=O)-Z-R¹⁴, hydroxy, mercapto, cyano, amino, mono- or di(C₁₋₄alkyl)amino, C₁₋₆alkyloxy optionally substituted with C(=O)-Z-R¹⁴, C₁₋₆alkylthio optionally substituted with C(=O)-Z-R¹⁴, C₁₋₆alkylsulfonyloxy, C₃₋₇cycloalkyl optionally substituted with C(=O)-Z-R¹⁴, aryl, aryloxy, arylthio, Het¹, Het¹oxy and Het¹thio; and if X is O, S or NR⁵, then R² may also represent aminothiocarbonyl, C₁₋₄alkylcarbonyl optionally substituted with C(=O)-Z-R¹⁴, C₁₋₄alkylthiocarbonyl optionally substituted with C(=O)-Z-R¹⁴, arylcarbonyl, arylthiocarbonyl,

Het¹carbonyl or Het¹thiocarbonyl;

R³ represents hydrogen, C₁₋₆alkyl or C₃₋₇cycloalkyl;

R⁴ represents hydrogen, C₁₋₆alkyl or C₃₋₇cycloalkyl; or

R^3 and R^4 taken together form a C_{2-6} alkanediyl;

R^5 represents hydrogen or C_{1-4} alkyl;

each R^6 independently represents C_{1-6} alkylsulfonyl, aminosulfonyl,

piperidinylsulfonyl, mono- or di(C_{1-4} alkyl)aminosulfonyl, mono- or

5 di(benzyl)aminosulfonyl, polyhalo C_{1-6} alkylsulfonyl, C_{1-6} alkylsulfinyl,

phenyl C_{1-4} alkylsulfonyl, piperazinylsulfonyl, aminopiperidinylsulfonyl,

piperidinyl-aminosulfonyl, N- C_{1-4} alkyl-N-piperidinylaminosulfonyl, $Y-R^{14}$, mono-

or di- (C_{1-4} alkyl)amino C_{1-4} alkylsulfonyl, Het⁶sulfonyl or C_{3-7} cycloalkylsulfonyl;

each R^7 and each R^8 are independently selected from hydrogen, C_{1-4} alkyl,

10 hydroxy C_{1-4} alkyl, mercapto- C_{1-4} alkyl, dihydroxy C_{1-4} alkyl, aryl, aryl C_{1-4} alkyl,

C_{1-4} alkyloxy C_{1-4} alkyl, C_{1-4} alkylcarbonyl, C_{1-4} alkyl-thiocarbonyl, arylcarbonyl,

arylthiocarbonyl, Het³thiocarbonyl, Het³carbonyl, mono- or di(C_{1-4} alkyl)amino C_{1-4}

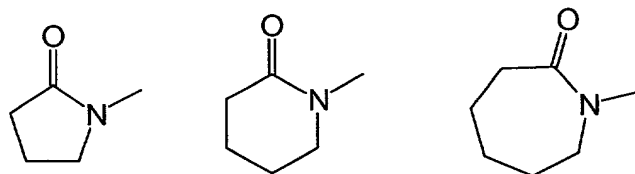
4alkyl, arylaminocarbonyl, arylaminothiocarbonyl, Het³aminocarbonyl,

Het³aminothiocarbonyl, C_{3-7} cycloalkyl, pyridinyl C_{1-4} alkyl,

15 C_{1-4} alkanediyl-C(=O)-Z- R^{14} , -C(=O)-Z- R^{14} , -Y- C_{1-4} alkanediyl-C(=O)-Z- R^{14} , Het³,

Het⁴ and R^6 ; or R^7 and R^8 taken together with the nitrogen atom to which they

are attached form a radical of formula



R^9 and R^{10} are each independently selected from hydrogen, C_{1-4} alkyl,

20 hydroxy C_{1-4} alkyl, mercapto- C_{1-4} alkyl, dihydroxy C_{1-4} alkyl, phenyl,

phenyl C_{1-4} alkyl, C_{1-4} alkyloxy C_{1-4} alkyl, C_{1-4} alkylcarbonyl, arylcarbonyl,

Het³carbonyl, Het³thiocarbonyl, mono- or di(C_{1-4} alkyl)amino C_{1-4} alkyl,

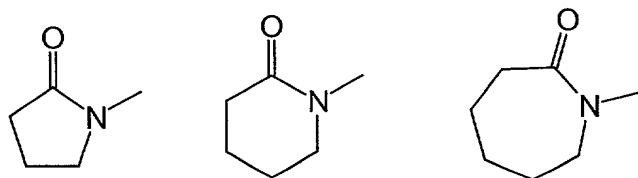
arylaminocarbonyl, arylaminothiocarbonyl, Het³aminocarbonyl,

Het³aminothiocarbonyl, C_{3-7} cycloalkyl, pyridinyl C_{1-4} alkyl,

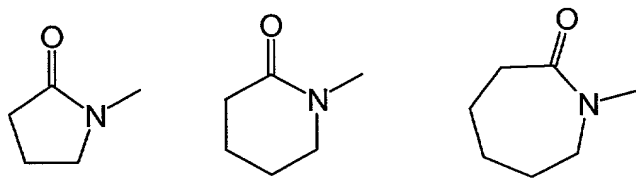
25 C_{1-4} alkanediyl-C(=O)-Z- R^{14} , -C(=O)-Z- R^{14} , -Y- C_{1-4} alkanediyl-C(=O)-Z- R^{14} , Het³,

Het⁴ and R^6 ; or R^9 and R^{10} taken together with the nitrogen atom to which they

are attached form a radical of formula

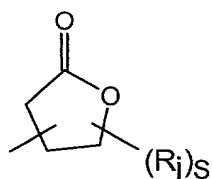


- each R^{11} independently being selected from hydroxy, mercapto, cyano, nitro, halo, trihalomethyl, C_{1-4} alkyloxy optionally substituted with $C(=O)-Z-R^{14}$, C_{1-6} alkylthio optionally substituted with $C(=O)-Z-R^{14}$, formyl,
- 5 trihalo C_{1-4} alkylsulfonyloxy, R^6 , NR^7R^8 , $C(=O)NR^{15}R^{16}$, $-C(=O)-Z-R^{14}$, $-Y-C_{1-4}$ alkanediyl- $C(=O)-Z-R^{14}$, aryl, aryloxy, arylcarbonyl, arylthiocarbonyl, C_{3-7} cycloalkyl optionally substituted with $C(=O)-Z-R^{14}$, C_{3-7} cycloalkyloxy optionally substituted with $C(=O)-Z-R^{14}$, C_{3-7} cycloalkylthio optionally substituted with $C(=O)-Z-R^{14}$, phthalimide-2-yl, Het³, Het⁴, $C(=O)Het^3$, $C(=O)C_{1-4}$ alkyl
- 10 optionally be substituted with one or more substituents independently selected from hydroxy, mercapto, halo and phenyl;
- R^{12} and R^{13} are each independently selected from hydrogen, C_{1-4} alkyl, hydroxy C_{1-4} alkyl, mercapto- C_{1-4} alkyl, dihydroxy C_{1-4} alkyl, phenyl, phenyl- C_{1-4} alkyl, C_{1-4} alkyloxy C_{1-4} alkyl, C_{1-4} alkylcarbonyl, C_{1-4} alkylthiocarbonyl,
- 15 arylcarbonyl, mono- or di(C_{1-4} alkyl)amino C_{1-4} alkyl, arylaminocarbonyl, arylaminothiocarbonyl, C_{3-7} cycloalkyl, pyridinyl C_{1-4} alkyl, C_{1-4} alkanediyl- $C(=O)-Z-R^{14}$, $-C(=O)-Z-R^{14}$, $-Y-C_{1-4}$ alkanediyl- $C(=O)-Z-R^{14}$ and R^6 ; or R^{12} and R^{13} taken together with the nitrogen atom to which they are attached form a radical of formula

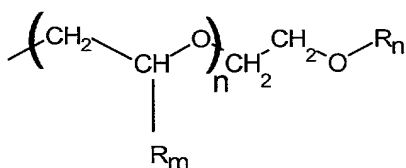


- 20 each R^{14} independently represents hydrogen; C_{1-20} acyl or C_{1-20} alkyl C_{1-20} acyl (having a straight or branched, saturated or unsaturated hydrocarbon chain having 1 to 20 carbon atoms) optionally substituted with one or more substituents selected from hydroxy, mercapto, hydroxy C_{1-4} alkyl, mercapto-
- 25 C_{1-4} alkyl, $NR^{17}R^{18}$, aryl, mono- or di-(C_{1-4} alkyl)amino, cyano and Het⁵;

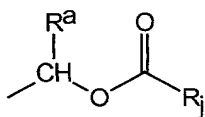
- C₁₋₂₀alkyl optionally substituted with one or more substituents selected from hydroxy, halo, mercapto, C₁₋₄alkyloxy, C₁₋₄alkoxy, mercaptoC₁₋₄alkyl, NR¹⁷R¹⁸, aryl, mono- or di-(C₁₋₄alkyl)amino, cyano, Het⁵, C₁₋₄alkyloxycarbonyl, arylC₁₋₄alkyloxycarbonyl, arylC₁₋₄alkoxy, arylC₁₋₄alkylthiocarbonyl, arylC₁₋₄alkylthio, Het⁵C₁₋₄alkoxy, arylC₁₋₄alkylthio, C₃₋₇ cycloalkyl and Het⁵C₁₋₄alkylthio; C₃₋₂₀alkenyl optionally substituted with phenyl; C₃₋₂₀alkynyl; C₃₋₇ cycloalkyl optionally substituted with one or more substituents selected from hydroxy, mercapto, halo, mercaptoC₁₋₄alkyl and hydroxyC₁₋₄alkyl; Het⁵ or phenyl or R¹⁴ represents a radical having any of the following formulae:



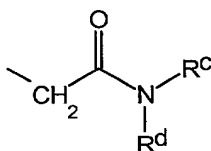
(a)



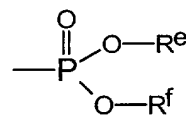
(b)



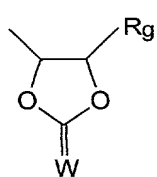
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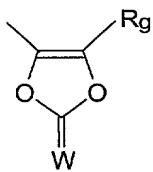
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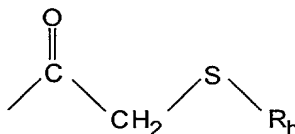
(e)



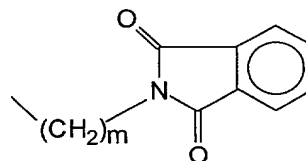
(h)



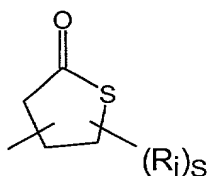
(i)



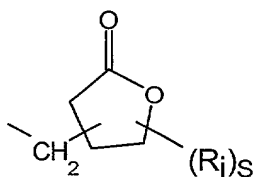
(j)



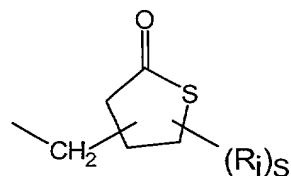
(k)



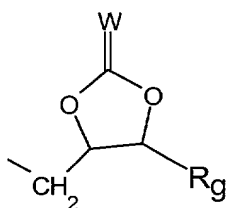
(l)



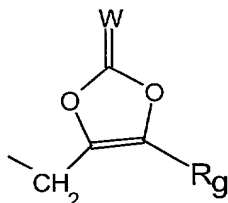
(m)



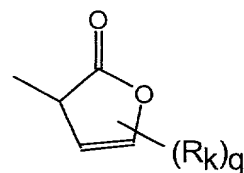
(n)



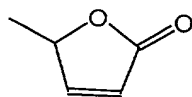
(o)



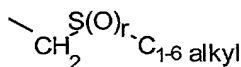
(p)



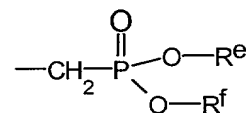
(q)



(r)



(s)



(t)

wherein m is 1 to 4, n is 0 to 5, q is 0 to 2, r is 0 to 2 and s is 0 to 4;

5 R^b is selected from hydrogen, C_{1-6} alkyl, phenyl, C_{3-7} cycloalkyl,

C_{1-4} alkyloxy C_{1-6} alkyl and C_{1-4} alkyl-Y- C_{1-4} alkyl;

R^a , R^c , R^d , R^e and R^f are each independently selected from hydrogen, C_{1-6} alkyl, phenyl and C_{3-7} cycloalkyl, or R^e and R^f taken together may form

-CH₂-CH₂-, -CH₂-CH₂-CH₂- or -CH₂-CH₂-CH₂-CH₂-;

10 R_g , R_h and R_k are each independently hydrogen or C_{1-4} alkyl;

R_i is selected from hydroxy, C_{3-7} cycloalkyl and C_{1-4} alkyl, or two R_i taken together may form -CH₂-CH₂-, -CH₂-CH₂-CH₂- or -CH₂-CH₂-CH₂-CH₂- (thus building a spiro radical);

R_j is selected from -O- R_b ; C_{1-6} alkyl optionally substituted with phenyl or

C₃₋₇cycloalkyl; phenyl; C₃₋₇cycloalkyl optionally substituted with C₁₋₄ alkyloxy and mono-or di(C₁₋₄alkyl)amino;

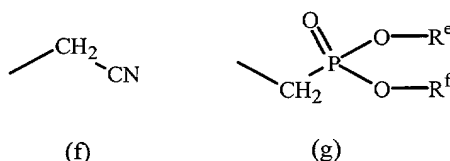
R_m is hydrogen or C₁₋₄ alkyloxy;

R_n is hydrogen, C₁₋₄alkyl, C₃₋₇cycloalkyl, phenyl or phenylC₁₋₄alkyl; and

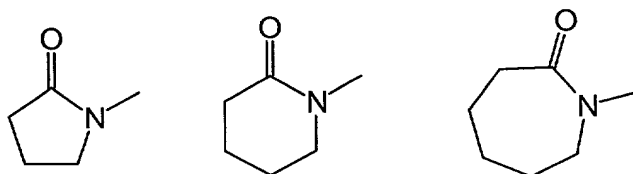
5 W represents O or S;

each Z independently represents O, S, NH, -CH₂-O- or -CH₂-S- whereby -CH₂- is attached to the carbonyl group; or

-Z-R¹⁴ taken together form a radical of formula



- 10 R¹⁵ and R¹⁶ are each independently selected from hydrogen; C₁₋₄alkyl optionally substituted with one or more substituents independently selected from hydroxy, mercapto, aryl, mono- or di(C₁₋₄alkyl) amino and pyridinyl; C₁₋₄alkyloxy; aryl; -C(=O)-Z-R¹⁴; arylcarbonyl; arylthiocarbonyl; arylaminocarbonyl; arylaminothiocarbonyl; aminocarbonylmethylene; mono- or di(C₁₋₄alkyl)
- 15 aminocarbonylmethylene; Het³aminocarbonyl; Het³aminothio-carbonyl; pyridinylC₁₋₄alkyl; Het³ and R⁶; or R¹⁵ and R¹⁶ taken together with the nitrogen atom to which they are attached form a radical of formula



- R¹⁷ and R¹⁸ are each independently selected from hydrogen, C₁₋₆alkyl
- 20 optionally substituted with one or more substituents independently selected from hydroxy, mercapto, aryl, mono- or di(C₁₋₄alkyl) amino, C₁₋₄ alkyloxy and pyridinyl;
- C₁₋₄alkyloxycarbonyl; aryl; C₁₋₄alkylcarbonyl; C₁₋₄alkylthiocarbonyl; arylcarbonyl; arylthiocarbonyl; arylaminocarbonyl; arylaminothiocarbonyl; C₃₋₇cycloalkyl;
- 25 C₁₋₄alkane-diyl-C(=O)-Z-C₁₋₆alkyl; -C(=O)-Z-C₁₋₆alkyl;

-Y-C₁₋₄alkanediyl-C(=O)-Z-C₁₋₆alkyl and R⁶;

aryl represents phenyl optionally substituted with one, two or three substituents each independently selected from nitro, azido, cyano, halo, hydroxy, mercapto, C₁₋₄alkyl, C₃₋₇cycloalkyl, C₁₋₄alkyloxy, C₁₋₄alkylthio, formyl, polyhaloC₁₋₄alkyl, NR⁹R¹⁰, C(=O)NR⁹R¹⁰, C(=O)-Z-R¹⁴, R⁶, -O-R⁶, phenyl, Het³, C(=O)Het³ and C₁₋₄alkyl substituted with one or more substituents each independently selected from halo, hydroxy, mercapto, C₁₋₄alkyloxy, C₁₋₄alkylthio, C(=O)-Z-R¹⁴, -Y-C₁₋₄alkanediyl-C(=O)-Z-R¹⁴, Het³ or NR⁹R¹⁰;

Het¹ represents a three-membered, four-membered, five-membered or six-membered aromatic or non-aromatic, monocyclic or polycyclic heterocycle comprising one or more, preferably one to four, heteroatoms, preferably selected from nitrogen, oxygen, sulfur and phosphorus, or a fused polycyclic ring system including such heterocycle (such as for instance a fused benzoheterocycle); non-limiting examples of such heterocycles include for instance pyrrolyl, pyrrolinyl, imidazolyl, imidazolinyl, pyrazolyl, pyrazolinyl, triazolyl, tetrazolyl, furanyl, tetrahydrofuranyl, thienyl, thiolanyl, dioxolanyl, oxazolyl, oxazolinyl, isoxazolyl, thiazolyl, thiazolinyl, isothiazolyl, thiadiazolyl, oxadiazolyl, pyridinyl, pyrimidinyl, pyrazinyl, pyranyl, pyridazinyl, pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl, thiomorpholinyl, dioxanyl, dithianyl, trithianyl, triazinyl, benzothienyl, isobenzothienyl, benzofuranyl, isobenzofuranyl, benzothiazolyl, benzoxazolyl, benzodioxanyl, indolyl, isoindolyl, indolinyl, purinyl, 1*H*-pyrazolo[3,4-*d*]pyrimidinyl, benzimidazolyl, quinolyl, isoquinolyl, cinnolinyl, phtalazinyl, quinazolinyl, quinoxalinyl, thiazolopyridinyl, oxazolopyridinyl and imidazo[2,1-*b*]thiazolyl; wherein said heterocycles each independently may optionally be substituted with one, or where possible, two or three substituents each independently selected from Het², R¹¹ and C₁₋₄alkyl optionally substituted with one or, where possible, two or three substituents each independently selected from Het² and R¹¹;

Het² represents a three-membered, four-membered, five-membered or six-membered aromatic or non-aromatic, monocyclic or polycyclic heterocycle comprising one or more, preferably one to four, heteroatoms, preferably selected from nitrogen, oxygen, sulfur and phosphorus, or a fused polycyclic

ring system including such heterocycle (such as for instance a fused benzoheterocycle); non-limiting examples of such heterocycles include for instance pyrrolyl, pyrrolinyl, imidazolyl, imidazolinyl, pyrazolyl, pyrazolinyl, triazolyl, tetrazolyl, furanyl, tetrahydrofuranyl, thienyl, thiolanyl, dioxolanyl, oxazolyl, oxazolinyl, isoxazolyl, thiazolyl, thiazolinyl, isothiazolyl, thiadiazolyl, oxadiazolyl, pyridinyl, pyrimidinyl, pyrazinyl, pyranyl, pyridazinyl, dioxanyl, dithianyl, trithianyl, triazinyl, benzothienyl, isobenzothienyl, benzofuranyl, isobenzofuranyl, benzothiazolyl, benzoxazolyl, indolyl, isoindolyl, indolinyl, purinyl, 1*H*-pyrazolo[3,4-*d*]pyrimidinyl, benzimidazolyl, quinolyl, isoquinolyl, cinnolinyl, phtalazinyl, quinazolinyl, quinoxalinyl, thiazolopyridinyl, oxazolopyridinyl and imidazo[2,1-*b*]thiazolyl; wherein said heterocycles each independently may optionally be substituted with one, or where possible, two or three substituents each independently selected from Het⁴, R¹¹ and C₁₋₄alkyl optionally substituted with one or, where possible, two or three substituents each independently selected from Het⁴ and R¹¹;

Het³ represents a three-membered, four-membered, five-membered or six-membered aromatic or non-aromatic monocyclic heterocycle comprising one or more, preferably one to four, heteroatoms, preferably selected from nitrogen, oxygen, sulfur and phosphorus; non-limiting examples of such heterocycles include for instance pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl, thiomorpholinyl, dioxolanyl and tetrahydropyranyl; wherein said monocyclic heterocycles each independently may optionally be substituted with, where possible, one, two, three or four substituents each independently selected from hydroxy, C₁₋₄alkyl, C₁₋₄alkyloxy, C₁₋₄alkylcarbonyl, piperidinyl, NR¹²R¹³, C(=O)-Z-R¹⁴, R⁶ and C₁₋₄alkyl substituted with one or two substituents independently selected from hydroxy, carbonyl C₁₋₄alkyloxy, phenyl, C(=O)-Z-R¹⁴, -Y-C₁₋₄alkanediyl-C(=O)-Z-R¹⁴, R⁶ and NR¹²R¹³;

Het⁴ represents a three-membered, four-membered, five-membered or six-membered aromatic or non-aromatic monocyclic heterocycle comprising one or more, preferably one to four, heteroatoms, preferably selected from nitrogen, oxygen, sulfur and phosphorus; non-limiting examples of such heterocycles include for instance pyrrolyl, imidazolyl, pyrazolyl, triazolyl, tetrazolyl, furanyl,

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thienyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, thiadiazolyl, oxadiazolyl, pyridinyl, pyrimidinyl, pyrazinyl, pyranyl, pyridazinyl and triazinyl;

Het⁵ represents a three-membered, four-membered, five-membered or six-membered aromatic or non-aromatic, monocyclic or polycyclic heterocycle

5 comprising one or more, preferably one to four, heteroatoms, preferably selected from nitrogen, oxygen, sulfur and phosphorus, or a fused polycyclic ring system including such heterocycle (such as for instance a fused benzoheterocycle); non-limiting examples of such heterocycles include for instance pyrrolyl, pyrrolinyl, imidazolyl, imidazolinyl, pyrazolyl, pyrazolinyl, 10 triazolyl, tetrazolyl, furanyl, tetrahydrofuranyl, thienyl, thiolanyl, dioxolanyl, oxazolyl, oxazolanyl, isoxazolyl, thiazolyl, thiazolinyl, isothiazolyl, thiadiazolyl, oxadiazolyl, pyridinyl, pyrimidinyl, pyrazinyl, pyranyl, pyridazinyl, pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl, thiomorpholinyl, tetrahydropyranyl, dioxanyl, dithianyl, trithianyl, triazinyl, benzothienyl, isobenzothienyl, 15 benzofuranyl, isobenzofuranyl, benzothiazolyl, benzoxazolyl, benzodioxanyl, indolyl, isoindolyl, indolinyl, purinyl, 1*H*-pyrazolo[3,4-*d*]pyrimidinyl, benzimidazolyl, quinolyl, isoquinolyl, cinnolinyl, phtalazinyl, quinazolinyl, quinoxalinyl, thiazolopyridinyl, oxazolopyridinyl and imidazo[2,1-*b*]thiazolyl;

wherein said heterocycles each independently may be substituted with, where 20 possible, one, two, three or four substituents each independently selected from hydroxy, mercapto, carbonyl, C₁₋₄alkyl, C₁₋₄alkyloxy, C₁₋₄alkylthio, C₁₋₄alkylcarbonyl, piperidinyl, NR¹⁷R¹⁸, C(=O)-Z-C₁₋₆alkyl, R⁶, sulfonamido and C₁₋₄alkyl substituted with one or two substituents independently selected from hydroxy, C₁₋₄alkyloxy, mercapto, C₁₋₄alkylthio, phenyl, C(=O)-Z-C₁₋₆alkyl, 25 -Y-C₁₋₄alkanediyl-C(=O)-Z-C₁₋₆alkyl, R⁶ and NR¹⁷R¹⁸ ;

Het⁶ represents a three-membered, four-membered, five-membered or six-membered aromatic or non-aromatic monocyclic heterocycle comprising one or more, preferably one to four, heteroatoms, preferably selected from nitrogen, oxygen, sulfur and phosphorus; non-limiting examples of such heterocycles 30 include for instance pyrrolidinyl, piperidinyl, azaridinyl, pyrazolinyl and pyrolinyl, wherein said heterocycle may optionally be substituted with one, or where possible, two or three substituents each independently selected from Het² , R¹¹

and C₁₋₄alkyl optionally substituted with one or more substituents independently selected from Het² and R¹¹.

provided however that

- R² is other than C₁₋₆ alkyloxycarbonylC₁₋₆alkyl or aminocarbonyl; and
- 5 • R⁷, R⁸, R⁹ and R¹⁰ are other than aminocarbonyl, C₁₋₄alkylcarbonyloxy-C₁₋₄alkylcarbonyl, hydroxyC₁₋₄alkylcarbonyl, C₁₋₄alkyloxycarbonylcarbonyl, C(=O)-O-R¹⁹, C₁₋₄alkanediylC(=O)-O-R¹⁹ or -Y-C₁₋₄alkanediylC(=O)-O-R¹⁹; and
- 10 • R¹² and R¹³ are other than C₁₋₄alkylcarbonyloxy-C₁₋₄alkylcarbonyl, hydroxyC₁₋₄alkylcarbonyl or C₁₋₄alkylcarbonylcarbonyl; and
- R¹¹ is other than C(=O)-O-R¹⁹, Y-C₁₋₄alkanediyl - C(=O)-OR¹⁹, C(=O)NH₂, C(=O)NHC₁₋₄alkyl or C(=O)NHC₃₋₇cycloalkyl; and
- R¹⁵ and R¹⁶ are other than aminocarbonyl, C₁₋₄alkylcarbonyloxy-C₁₋₄alkylcarbonyl, hydroxy C₁₋₄alkylcarbonyl or C₁₋₄alkyloxycarbonylcarbonyl; and
- 15 • aryl is other than phenyl substituted with C(=O)-O-R¹⁹, C(=O)NH₂, C(=O)NHC₁₋₄alkyl, C(=O)NHC₃₋₇cycloalkyl and/or with C₁₋₄alkyl substituted with C(=O)-O-R¹⁹ or Y-C₁₋₄alkanediyl - C(=O)-O-R¹⁴; and
- Het³ is other than a monocyclic heterocycle substituted with
- 20 C(=O)-O-R¹⁹ and/or with C₁₋₄alkyl substituted with C(=O)-O-R¹⁹ and/or Y-C₁₋₄alkanediyl C(=O)-O-R¹⁹; and
- in each of the above proviso's R¹⁹ is defined as hydrogen, C₁₋₄alkyl, C₃₋₇cycloalkyl, aminocarbonylmethylene or mono- or di(C₁₋₄alkyl)aminocarbonylmethylene; and

25 wherein the said compound having the formula (I) contains at least one -C(=O)-Z-R¹⁴ moiety.

As used in the foregoing definitions and hereinafter:

- the term "halo" is generic to fluoro, chloro, bromo and iodo;
- the term "C₃₋₇cycloalkyl" is generic to cyclopropyl, cyclobutyl, cyclopentyl,
- 30 cyclohexyl and cycloheptyl;
- the term "C₁₋₄alkyl" defines straight and branched chain saturated

hydrocarbon radicals having from 1 to 4 carbon atoms such as, for example, methyl, ethyl, propyl, butyl, 1-methylethyl, 2-methylpropyl, 2,2-dimethylethyl and the like;

- the term "C₁₋₆alkyl" is meant to include C₁₋₄alkyl and the higher homologues thereof having 5 or 6 carbon atoms such as, for example, pentyl, 2-methylbutyl, hexyl, 2-methylpentyl and the like;
- the term "C₁₋₂₀alkyl" is meant to include C₁₋₆alkyl and the higher homologues thereof having 7 to 20 carbon atoms such as, for example, heptyl, octyl, nonyl, decyl, undecyl, dodecyl, tridecyl, tetradecyl, pentadecyl, octadecyl, nonadecyl, eicosyl and the like;
- the term "C₅₋₂₀alkyl" is meant to include C₁₋₂₀alkyl except for C₁₋₄alkyl;
- the term "C₃₋₂₀alkenyl" defines straight and branched chain hydrocarbon radicals containing one double bond and having from 3 to 20 carbon atoms such as, for example, 2-propenyl, 3-butenyl, 2-butenyl, 2-pentenyl, 3-pentenyl, 3-methyl-2-butenyl, 3-hexenyl and the like, the carbon atom of the said C₃₋₂₀alkenyl connected to the remainder of the molecule being preferably saturated;
- the term "C₃₋₂₀alkynyl" defines straight and branched chain hydrocarbon radicals containing one triple bond and having from 3 to 20 carbon atoms such as, for example, 2-propynyl, 3-butyne, 2-butyne, 2-pentyne, 3-pentyne, 3-methyl-2-butyne, 3-hexynyl and the like, the carbon atom of the said C₃₋₂₀alkynyl connected to the remainder of the molecule being preferably saturated;
- the term "polyhaloC₁₋₄alkyl" is defined as polyhalosubstituted C₁₋₄alkyl, in particular C₁₋₄alkyl substituted with 1 to 6 halogen atoms, more particularly difluoro- or trifluoromethyl;
- the term "polyhaloC₁₋₆alkyl" is defined as polyhalosubstituted C₁₋₆alkyl;
- the term "polyhaloC₁₋₂₀alkyl" is defined as polyhalosubstituted C₁₋₂₀alkyl;
- the term "C₁₋₄alkanediyl" defines bivalent straight or branch chained alkanediyl radicals having from 1 to 4 carbon atoms such as, for example, methylene, 1,2-ethanediyl, 1,3-propanediyl, 1,4-butanediyl and the like;
- the term "C₂₋₆alkanediyl" defines bivalent straight or branch chained

alkanediyl radicals having from 2 to 6 carbon atoms such as, for example, 1,2-ethanediyl, 1,3-propanediyl, 1,4-butanediyl, 1,5-pentanediyl, 1,6-hexanediyl and the like.

Het¹, Het², Het³, Het⁴ and Het⁵ are meant to include all possible isomeric forms of the heterocycles mentioned in the above definitions, for instance pyrrolyl also includes 2*H*-pyrrolyl; triazolyl includes 1,2,4-triazolyl and 1,3,4-triazolyl; oxadiazolyl includes 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl, 1,2,5-oxadiazolyl and 1,3,4-oxadiazolyl; thiadiazolyl includes 1,2,3-thiadiazolyl, 1,2,4-thiadiazolyl, 1,2,5-thiadiazolyl and 1,3,4-thiadiazolyl; pyranyl includes 2*H*-pyranyl and 4*H*-pyranyl.

The heterocycles represented by Het¹, Het², Het³, Het⁴ and Het⁵ may be attached to the remainder of the molecule of formula (I) through any ring carbon or heteroatom as appropriate. Thus, for example, when the heterocycle is imidazolyl, it may be a 1-imidazolyl, 2-imidazolyl, 4-imidazolyl and 5-imidazolyl; when it is thiazolyl, it may be 2-thiazolyl, 4-thiazolyl and 5-thiazolyl; when it is triazolyl, it may be 1,2,4-triazol-1-yl, 1,2,4-triazol-3-yl, 1,2,4-triazol-5-yl, 1,3,4-triazol-1-yl and 1,3,4-triazol-2-yl; when it is benzothiazolyl, it may be 2-benzothiazolyl, 4-benzothiazolyl, 5-benzothiazolyl, 6-benzothiazolyl and 7-benzothiazolyl.

The C₁₋₂₀acyl is derived from :

acetic acid	CH ₃ COOH	tridecanoic acid	C ₁₂ H ₂₅ COOH
propionic acid	C ₂ H ₅ COOH	myristic acid	C ₁₃ H ₂₇ COOH
butyric acid	C ₃ H ₇ COOH	pentadecanoic acid	C ₁₄ H ₂₉ COOH
valeric acid	C ₄ H ₉ COOH	palmitic acid	C ₁₅ H ₃₁ COOH
hexanoic acid	C ₅ H ₁₁ COOH	heptadecanoic acid	C ₁₆ H ₃₃ COOH
heptanoic acid	C ₆ H ₁₃ COOH	stearic acid	C ₁₇ H ₃₅ COOH
octanoic acid	C ₇ H ₁₅ COOH	oleic acid	C ₁₇ H ₃₃ COOH
nonanoic acid	C ₈ H ₁₇ COOH	linolic acid	C ₁₇ H ₃₁ COOH
decanoic acid	C ₉ H ₁₉ COOH	linolenic acid	C ₁₇ H ₂₉ COOH
undecanoic acid	C ₁₀ H ₂₁ COOH	nonadecanoic acid	C ₁₈ H ₃₇ COOH
lauric acid	C ₁₁ H ₂₃ COOH	icosanoic acid	C ₁₉ H ₃₉ COOH

The pharmaceutically acceptable addition salts as mentioned hereinabove are meant to comprise the therapeutically active non-toxic acid addition salt forms which the compounds having the formula (I) are able to form. The latter can conveniently be obtained by treating the base form with such appropriate acids as inorganic acids, for example, hydrohalic acids, e.g. hydrochloric, hydrobromic and the like; sulfuric acid; nitric acid; phosphoric acid and the like; or organic acids, for example, acetic, propanoic, hydroxyacetic, 2-hydroxypropanoic, 2-oxopropanoic, ethanedioic, propanedioic, butanedioic, 2-butenedioic, 2-butenedioic, 2-hydroxybutanedioic, 2,3-dihydroxybutanedioic, 2-hydroxy-1,2,3-propanetricarboxylic, methanesulfonic, ethanesulfonic, benzenesulfonic, 4-methylbenzenesulfonic, cyclohexanesulfamic, 2-hydroxybenzoic, 4-amino-2-hydroxybenzoic and the like. Conversely the salt form can be converted by treatment with alkali into the free base form.

Compounds having the formula (I) which contain acidic protons may be converted into their therapeutically active non-toxic metal or amine addition salt forms by treatment with appropriate organic and inorganic bases. Appropriate base salt forms comprise, for example, the ammonium salts, the alkali and earth alkaline metal salts, e.g. the lithium, sodium, potassium, magnesium, calcium salts and the like, salts with organic bases, e.g. the benzathine, *N*-methyl-D-glucamine, 2-amino-2-(hydroxymethyl)-1,3-propanediol, hydrabamine salts, and salts with naturally occurring amino-acids such as, for example, arginine, lysine and the like. Conversely the salt form can be converted by treatment with an acid into the free acid form. The term addition salt also comprises the hydrates and solvent addition forms of such salts which the compounds having the formula (I) are able to form. Examples of such forms are e.g. hydrates, alcoholates and the like.

The N-oxide forms of the present compounds are meant to comprise compounds having the formula (I), wherein one or several nitrogen atoms are oxidized to the so-called N-oxide. For example, one or more nitrogen atoms of any of the heterocycles in the definition of Het¹, Het², Het³, Het⁴ and Het⁵ may be N-oxidized.

Some of the compounds of formula (I) may also exist in their tautomeric forms. Such forms although not explicitly indicated in the above formula are intended to be included within the scope of the present invention. For example, a hydroxy substituted triazine moiety may also exist as the corresponding triazinone moiety; a hydroxy substituted pyrimidine moiety may also exist as the corresponding pyrimidinone moiety.

The term "stereochemically isomeric forms" as used hereinbefore defines all the possible stereoisomeric forms in which the compounds of formula (I) can exist. Unless otherwise mentioned or indicated, the chemical designation of compounds denotes the mixture of all possible stereochemically isomeric forms, said mixtures containing all diastereomers and enantiomers of the basic molecular structure. More in particular, stereogenic centers may have the R- or S-configuration, used herein in accordance with Chemical Abstracts nomenclature. Stereochemically isomeric forms of the compounds of formula (I) certainly are intended to be embraced within the scope of this invention.

The compounds of formula (I) and some of the intermediates in the present invention contain one or more asymmetric carbon atoms. The pure and mixed stereochemically isomeric forms of the compounds of formula (I) are also intended to be embraced within the scope of the present invention. Whenever used hereinafter, the term "compounds of formula (I)" is meant to also include their N-oxide forms, their pharmaceutically acceptable addition salts, and their stereochemically isomeric forms.

An interesting group of compounds are those compounds of formula (I) wherein the 6-azauracil moiety is connected to the phenyl ring in the para or meta position relative to the carbon atom bearing the $-X-R^2$, R^3 and R^4 substituents; preferably in the para position. Another interesting group contains those compounds of formula (I) wherein one or more of the following restrictions apply :

- ♦ p is 0, 1 or 2;
- ♦ X is S, NR^5 or a direct bond; more preferably a direct bond;
- ♦ each R^1 independently is halo, polyhalo C_{1-6} alkyl, C_{1-6} alkyl, C_{1-}

alkyloxy or aryl, preferably, chloro or trifluoromethyl, more preferably chloro;

- the at least one $-C(=O)-Z-R^{14}$ moiety contained by the compound of formula (I) is born by R^2 ,

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- R^2 is Het^1 or C_{1-6} alkyl substituted with one or two substituents selected from hydroxy, cyano, amino, mono- or di(C_{1-4} alkyl)amino, $C(=O)-Z-R^{14}$, C_{1-6} alkyloxy optionally substituted with $C(=O)-Z-R^{14}$, C_{1-6} alkylsulfonyloxy, C_{3-7} cycloalkyl optionally substituted with $C(=O)-Z-R^{14}$, aryl, aryloxy, arylthio, Het^1 , Het^1 oxy and Het^1 thio; and if X is O, S or NR⁵, then R^2 may also represent aminothiocarbonyl, C_{1-4} alkylcarbonyl optionally substituted with $C(=O)-Z-R^{14}$, C_{1-4} alkylthiocarbonyl optionally substituted with $C(=O)-Z-R^{14}$, arylcarbonyl, arylthiocarbonyl, Het^1 carbonyl or Het^1 thiocarbonyl; more preferably R^2 is Het^1 ;

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- R^3 is hydrogen, methyl, ethyl, propyl or cyclohexyl, more preferably methyl;

- R^4 is hydrogen or methyl, more preferably methyl;

- R^3 and R^4 are taken together to form a 1,4-butanediyl;

- R^6 is C_{1-6} alkylsulfonyl, aminosulfonyl or Het^6 sulfonyl, more preferably Het^6 sulfonyl;

20

- R^7 and R^8 are each independently hydrogen, C_{1-4} alkyl, Het^3 or R^6 ;

- R^9 and R^{10} are each independently hydrogen, C_{1-4} alkyloxy C_{1-4} alkyl, C_{1-4} alkylcarbonyl, aminocarbonyl, Het^3 carbonyl, Het^3 or R^6 ;

25

- R^{11} is cyano, nitro, halo, C_{1-4} alkyloxy, formyl, NR^7R^8 , $C(=O)NR^{15}R^{16}$, $-C(=O)-Z-R^{14}$, aryl, arylcarbonyl, Het^3 or $C(=O)Het^3$; more preferably R^{11} is phenyl, $-C(=O)-O-R^{14}$, $-C(=O)-S-R^{14}$ or $-C(=O)-NH-R^{14}$.

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- each R^{11} independently being selected from hydroxy, mercapto, cyano, nitro, halo, trihalomethyl, C_{1-4} alkyloxy optionally substituted with $C(=O)-Z-R^{14}$, C_{1-6} alkylthio optionally substituted with $C(=O)-Z-R^{14}$, formyl, trihalo C_{1-4} alkylsulfonyloxy, R^6 , NR^7R^8 , $C(=O)NR^{15}R^{16}$, $-C(=O)-Z-R^{14}$, $-Y-C_{1-4}$ alkanediyl- $C(=O)-Z-R^{14}$, aryl, aryloxy, arylcarbonyl, arylthiocarbonyl, C_{3-7} cycloalkyl optionally substituted with $C(=O)-Z-R^{14}$,

C₃₋₇cycloalkyloxy optionally substituted with C(=O)-Z-R¹⁴, C₃₋₇cycloalkylthio optionally substituted with C(=O)-Z-R¹⁴, phthalimide-2-yl, Het³, C(=O)Het³, C(=O)C₁₋₄alkyl optionally be substituted with one or more substituents independently selected from hydroxy, mercapto, halo and phenyl;

• R¹⁴ is dihydrofuranyl, C₅₋₂₀alkyl, C₃₋₂₀alkenyl, polyhaloC₁₋₆alkyl, Het⁵, a radical of formula (a) or C₁₋₂₀alkyl substituted with one or more substituents selected from phenyl, C₁₋₄alkylamino, cyano, Het¹, Het⁵, hydroxy and C₃₋₇cycloalkyl, more preferably a radical of formula (a) in which R_j is C₁₋₆alkyl and s is 2, or C₁₋₂₀alkyl substituted with hydroxy or Het⁵;

• R¹⁷ and R¹⁸ are each independently hydrogen or phenyl;

• aryl is phenyl optionally substituted with one, two or three substituents each independently selected from nitro, cyano, halo, hydroxy, C₁₋₄alkyl, C₃₋₇cycloalkyl, C₁₋₄alkyloxy, formyl, polyhaloC₁₋₄alkyl, NR⁹R¹⁰, C(=O)NR⁹R¹⁰, C(=O)-O-R¹⁴, -O-R⁶, phenyl, C(=O)Het³ and C₁₋₄alkyl substituted with one or more substituents each independently selected from halo, hydroxy, C₁₋₄alkyloxy, C(=O)-Z-R¹⁴, Het³ and NR⁹R¹⁰;

• Het¹ is a monocyclic heterocycle selected from pyrrolyl, imidazolyl, pyrazolyl, triazolyl, tetrazolyl, furanyl, thienyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, thiadiazolyl, oxadiazolyl, pyridinyl, pyrimidinyl, pyrazinyl, pyranyl, pyridazinyl and triazinyl, in particular imidazolyl, oxadiazolyl, thiazolyl, pyrimidinyl or pyridinyl, wherein said monocyclic heterocycles each independently may optionally be substituted with one, or where possible, two or three substituents each independently selected from Het², R¹¹ and C₁₋₄alkyl optionally substituted with Het² or R¹¹; more preferably Het¹ is imidazolyl, oxadiazolyl, thiazolyl or pyridinyl, especially thiazolyl, each independently and optionally substituted with one, or where possible, two or three substituents each independently selected from Het², R¹¹ and C₁₋₄alkyl optionally substituted with Het² or R¹¹, more preferably two substituents each independently selected from R¹¹ and C₁₋₄alkyl substituted with R¹¹;

• Het² is an aromatic heterocycle; more in particular furanyl, thienyl, pyridinyl or benzothienyl, wherein said aromatic heterocycles each independently may optionally be substituted with one, or where possible, two or three substituents each independently selected from R¹¹ and C₁₋₄alkyl;

• Het³ is piperidinyl, piperazinyl, morpholinyl or tetrahydropyranyl each independently and optionally substituted with, where possible, one, two, three or four substituents each independently selected from hydroxy, C₁₋₄alkyl, C₁₋₄alkylcarbonyl, piperidinyl and C₁₋₄alkyl substituted with one or two substituents independently selected from hydroxy, C₁₋₄alkyloxy and phenyl;

• Het⁴ is thienyl;

• Het⁵ is piperidinyl or piperazinyl optionally substituted with C₁₋₄alkyl, sulfonamido or R⁶, more preferably R⁶;

• Het⁶ is pyrrolidinyl.

Particular compounds are those compounds of formula (I) wherein p is 2 and both R¹ substituents are chloro; more preferably the two chloro substituents are in the ortho positions relative to the carbon atom bearing the -X-R², R³ and R⁴ substituents.

Other particular compounds are those compounds of formula (I) wherein the 6-azauracil moiety is in the para position relative to the carbon atom bearing the -X-R², R³ and R⁴ substituents, and p is 2 whereby both R¹ substituents are chloro positioned ortho relative to the carbon atom bearing the -X-R², R³ and R⁴ substituents.

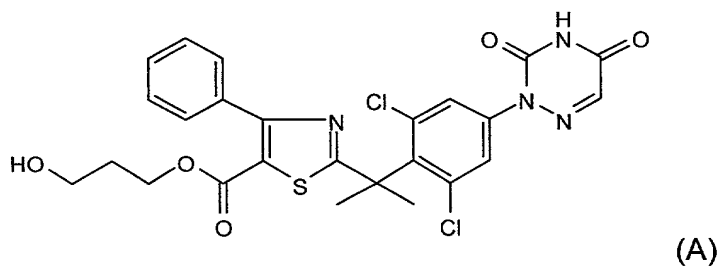
Other particular compounds are those compounds of formula (I) wherein X is a direct bond and R² is a monocyclic heterocycle selected from pyrrolyl, imidazolyl, pyrazolyl, triazolyl, tetrazolyl, furanyl, thienyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, thiadiazolyl, oxadiazolyl, pyridinyl, pyrimidinyl, pyrazinyl, pyranlyl, pyridazinyl and triazinyl, in particular imidazolyl, oxadiazolyl, thiazolyl, pyrimidinyl or pyridinyl, wherein said monocyclic heterocycles each independently may optionally be substituted with one, or where possible, two or three substituents each independently selected from Het², R¹¹ and C₁₋₄alkyl

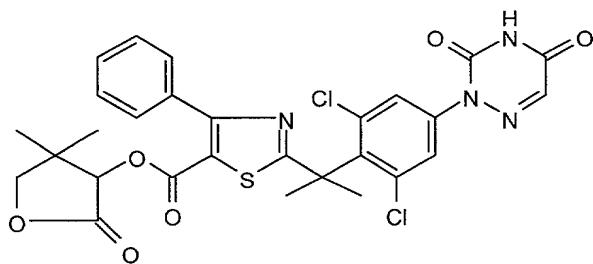
optionally substituted with Het² or R¹¹; more in particular R² is optionally substituted thiazolyl, pyridinyl or oxadiazolyl.

Preferred compounds are those compounds of formula (I) wherein R³ and R⁴ are both methyl and -X-R² is Het¹ wherein Het¹ suitably is optionally substituted thiazolyl, pyridinyl or oxadiazolyl.

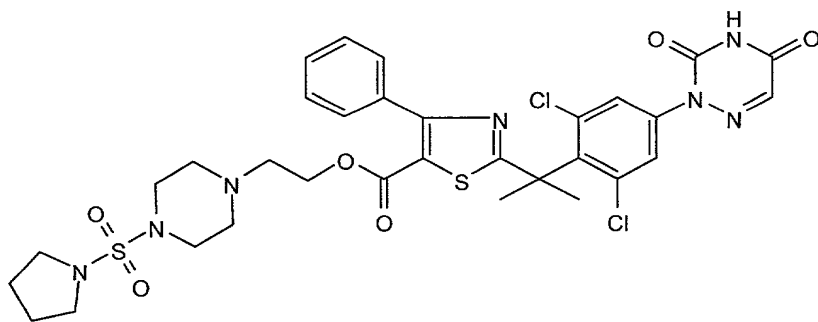
More preferred compounds are those compounds of formula (I) wherein R³ and R⁴ are both methyl, -X-R² is optionally substituted 2-thiazolyl or 3-oxadiazolyl, the 6-azauracil moiety is in the para position relative to the carbon atom bearing the -X-R², R³ and R⁴ substituents, and p is 2 whereby both R¹ substituents are chloro positioned ortho relative to the carbon atom bearing the -X-R², R³ and R⁴ substituents. Particularly preferred such compounds are those in which -X-R² is di-substituted with phenyl and either (i) R¹¹ where R¹¹ is a group of formula -C(=O)-Z-R¹⁴ in which Z is O and R¹⁴ is C₁₋₂₀alkyl substituted with hydroxy or with Het⁵ especially where Het⁵ is piperazinyl substituted with Het⁶sulfonyl, especially where Het⁶ is pyrrolidinyl, or R¹⁴ is a radical of formula (a) in which R_j is C₁₋₆alkyl and s is 2, or (ii) C₁₋₄alkyl substituted with R¹¹ where R¹¹ is a group of formula -C(=O)-Z-R¹⁴ in which Z is O and R¹⁴ is a radical of formula (a) in which R_j is C₁₋₆alkyl and s is 2.

Particularly preferred compounds are those of formulae (A), (B), (C) and (D) below:

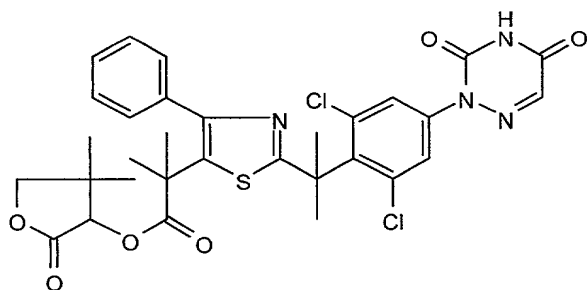




(B)



(C)



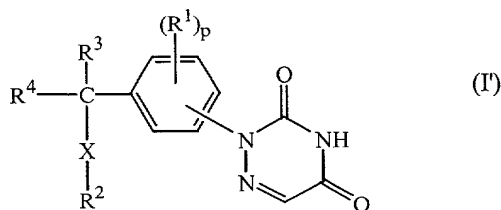
(D)

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Examples of compounds of formula (I) further includes compounds of formula (I') in which p, X, Y, R¹, R², R³, R⁴, R⁵, R⁶, R⁷, R⁸, R⁹, R¹⁰, R¹¹, R¹², R¹³, R¹⁴, n, m, R^a, R^b, R^c, R^d, R^e, R^f, R_g, R_h, R¹⁵, R¹⁶, Z, aryl, 'Het¹', Het², Het³, Het⁴ as used in relation to compounds of formula (1') have the meanings below:

The present invention is concerned with the compounds of formula



the *N*-oxides, the pharmaceutically acceptable addition salts and the stereochemically

isomeric forms thereof, wherein :

5 p represents an integer being 0, 1, 2, 3 or 4;

X represents O, S, NR^5 or a direct bond or $-X-R^2$ taken together may represent cyano;

Y represents O, S, NR^5 , or $S(O)_2$;

each R^1 independently represents $C(=O)-Z-R^{14}$, C_{1-6} alkyl, halo, polyhalo-

10 C_{1-6} alkyl, hydroxy, mercapto, C_{1-6} alkyloxy, C_{1-6} alkylthio, C_{1-6} alkylcarbonyloxy, aryl, cyano, nitro, Het³, R^6 , NR^7R^8 or C_{1-4} alkyl substituted with $C(=O)-Z-R^{14}$, Het³, R^6 or NR^7R^8 ;

R^2 represents Het¹, C_{3-7} cycloalkyl optionally substituted with $C(=O)-Z-R^{14}$,

15 C_{1-6} alkyl or C_{1-6} alkyl substituted with one or two substituents selected from $C(=O)-Z-R^{14}$, hydroxy, cyano, amino, mono- or di(C_{1-4} alkyl)amino, C_{1-6} alkyloxy optionally substituted with $C(=O)-Z-R^{14}$, C_{1-6} alkylsulfonyloxy, C_{3-7} cycloalkyl optionally substituted with $C(=O)-Z-R^{14}$, aryl, aryloxy, arylthio, Het¹, Het¹oxy and Het¹thio; and if X is O, S or NR^5 , then R^2 may also

20 represent aminothiocarbonyl, C_{1-4} alkylcarbonyl optionally substituted with $C(=O)-Z-R^{14}$, C_{1-4} alkylthiocarbonyl optionally substituted with $C(=O)-Z-R^{14}$, arylcarbonyl, arylthiocarbonyl, Het¹carbonyl or Het¹thiocarbonyl;

R^3 represents hydrogen, C_{1-6} alkyl or C_{3-7} cycloalkyl;

R^4 represents hydrogen, C_{1-6} alkyl or C_{3-7} cycloalkyl; or

R^3 and R^4 taken together form a C_{2-6} alkanediyl;

25 R^5 represents hydrogen or C_{1-4} alkyl;

each R^6 independently represents C_{1-6} alkylsulfonyl, aminosulfonyl, mono- or di(C_{1-4} alkyl)aminosulfonyl, mono- or di(benzyl)aminosulfonyl,

polyhaloC₁₋₆alkylsulfonyl, C₁₋₆alkylsulfinyl, phenylC₁₋₄alkylsulfonyl,
piperazinylsulfonyl, aminopiperidinylsulfonyl, piperidinylaminosulfonyl, *N*-C₁₋₄
alkyl-*N*-piperidinylaminosulfonyl or mono- or di(C₁₋₄alkyl)aminoC₁₋₄alkylsulfonyl;
each R⁷ and each R⁸ are independently selected from hydrogen, C₁₋₄alkyl,

5 hydroxyC₁₋₄alkyl, dihydroxyC₁₋₄alkyl, aryl, arylC₁₋₄alkyl, C₁₋₄alkyloxyC₁₋₄alkyl,
C₁₋₄alkylcarbonyl, arylcarbonyl, Het³carbonyl, mono- or di(C₁₋₄alkyl)amino-
C₁₋₄alkyl, arylaminocarbonyl, arylaminothiocarbonyl, Het³aminocarbonyl,
Het³aminothiocarbonyl, C₃₋₇cycloalkyl, pyridinylC₁₋₄alkyl, C₁₋₄alkanediyl-
C(=O)-Z-R¹⁴, -C(=O)-Z-R¹⁴, -Y-C₁₋₄alkanediyl-C(=O)-Z-R¹⁴, Het³ and R⁶;

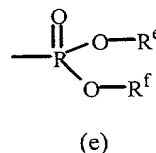
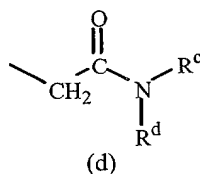
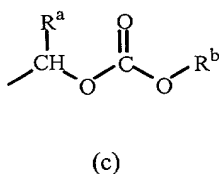
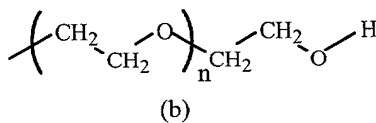
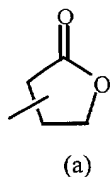
10 R⁹ and R¹⁰ are each independently selected from hydrogen, C₁₋₄alkyl, hydroxy-
C₁₋₄alkyl, dihydroxyC₁₋₄alkyl, phenyl, phenylC₁₋₄alkyl, C₁₋₄alkyloxyC₁₋₄alkyl,
C₁₋₄alkylcarbonyl, phenylcarbonyl, Het³carbonyl, mono- or di(C₁₋₄alkyl)amino-
C₁₋₄alkyl, phenylaminocarbonyl, phenylaminothiocarbonyl, Het³aminocarbonyl,
Het³aminothiocarbonyl, C₃₋₇cycloalkyl, pyridinylC₁₋₄alkyl,
15 C₁₋₄alkanediyl-C(=O)-Z-R¹⁴, -C(=O)-Z-R¹⁴, -Y-C₁₋₄alkanediyl-C(=O)-Z-R¹⁴,
Het³ and R⁶;

each R¹¹ independently being selected from hydroxy, mercapto, cyano, nitro,
halo, trihalomethyl, C₁₋₄alkyloxy optionally substituted with C(=O)-Z-R¹⁴,
formyl, trihaloC₁₋₄alkylsulfonyloxy, R⁶, NR⁷R⁸, C(=O)NR¹⁵R¹⁶, -C(=O)-Z-R¹⁴,
20 -Y-C₁₋₄alkanediyl-C(=O)-Z-R¹⁴, aryl, aryloxy, arylcarbonyl, C₃₋₇cycloalkyl
optionally substituted with C(=O)-Z-R¹⁴, C₃₋₇cycloalkyloxy optionally substituted
with C(=O)-Z-R¹⁴, phthalimide-2-yl, Het³, Het⁴ and C(=O)Het³;

R¹² and R¹³ are each independently selected from hydrogen, C₁₋₄alkyl, hydroxy-
C₁₋₄alkyl, dihydroxyC₁₋₄alkyl, phenyl, phenylC₁₋₄alkyl, C₁₋₄alkyloxyC₁₋₄alkyl,
25 C₁₋₄alkylcarbonyl, phenylcarbonyl, mono- or di(C₁₋₄alkyl)aminoC₁₋₄alkyl,
phenylaminocarbonyl, phenylaminothiocarbonyl, C₃₋₇cycloalkyl, pyridinyl-
C₁₋₄alkyl, C₁₋₄alkanediyl-C(=O)-Z-R¹⁴, -C(=O)-Z-R¹⁴,
-Y-C₁₋₄alkanediyl-C(=O)-Z-R¹⁴ and R⁶;

each R¹⁴ independently represents C₁₋₄ alkyl substituted with one or more
30 substituents selected from phenyl, di- C₁₋₄alkylamino, cyano, Het¹ and
C₃₋₇ cycloalkyl, hydrogen, C₁₋₂₀acyl (having a straight or branched, saturated

or unsaturated hydrocarbon chain having 1 to 20 carbon atoms), C₁₋₂₀alkyl, C₃₋₇cycloalkyl, polyhaloC₁₋₂₀alkyl or a radical of formula

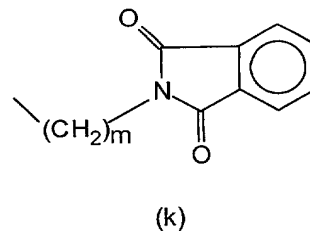
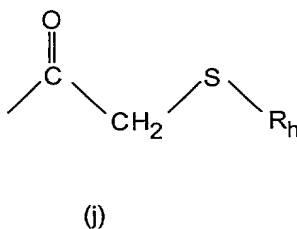
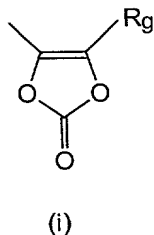
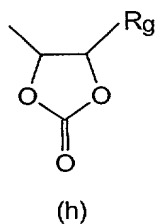


wherein n is 0 to 5;

R^a, R^b, R^c, R^d, R^e and R^f are each independently hydrogen,

C₁₋₆alkyl or C₃₋₇cycloalkyl; or

R^e and R^f taken together may form -CH₂-CH₂-, -CH₂-CH₂-CH₂- or -CH₂-CH₂-CH₂-CH₂-; or a radical of formula

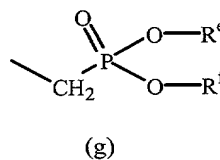
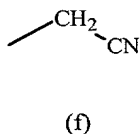


wherein m is 1 to 4

R_g and R_h are each independently C₁₋₄ alkyl;

each Z independently represents O, S, NH, -CH₂-O- or -CH₂-S- whereby -CH₂- is attached to the carbonyl group;

-Z-R¹⁴ taken together form a radical of formula



R¹⁵ and R¹⁶ are each independently selected from dihydroxyC₁₋₄alkyl, aryl, arylC₁₋₄alkyl, C₁₋₄alkyloxyC₁₋₄alkyl, -C(=O)-Z-R¹⁴, arylcarbonyl, mono- or

di(C₁₋₄alkyl)aminoC₁₋₄alkyl, arylaminocarbonyl, arylaminothiocarbonyl,
Het³aminocarbonyl, Het³aminothiocarbonyl, pyridinylC₁₋₄alkyl, Het³ or R⁶;
aminocarbonylmethylene or mono-or di(C₁₋₄alkyl)aminocarbonylmethylene;
aryl represents phenyl optionally substituted with one, two or three substituents
5 each independently selected from nitro, azido, cyano, halo, hydroxy,
C₁₋₄alkyl, C₃₋₇cycloalkyl, C₁₋₄alkyloxy, formyl, polyhaloC₁₋₄alkyl, NR⁹R¹⁰,
C(=O)NR⁹R¹⁰, C(=O)-Z-R¹⁴, R⁶, -O-R⁶, phenyl, Het³, C(=O)Het³ and C₁₋₄alkyl
substituted with one or more substituents each independently selected from
halo, hydroxy, C₁₋₄alkyloxy, C(=O)-Z-R¹⁴, -Y-C₁₋₄alkanediyl-C(=O)-Z-R¹⁴, Het³
10 or NR⁹R¹⁰;
Het¹ represents a heterocycle selected from pyrrolyl, pyrrolinyl, imidazolyl,
imidazolinyl, pyrazolyl, pyrazolinyl, triazolyl, tetrazolyl, furanyl,
tetrahydrofuranyl, thienyl, thiolanyl, dioxolanyl, oxazolyl, oxazolinyl, isoxazolyl,
thiazolyl, thiazolinyl, isothiazolyl, thiadiazolyl, oxadiazolyl, pyridinyl, pyrimidinyl,
15 pyrazinyl, pyranyl, pyridazinyl, pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl,
thiomorpholinyl, dioxanyl, dithianyl, trithianyl, triazinyl, benzothienyl,
isobenzothienyl, benzofuranyl, isobenzofuranyl, benzothiazolyl, benzoxazolyl,
indolyl, isoindolyl, indolinyl, purinyl, 1*H*-pyrazolo[3,4-*d*]pyrimidinyl,
benzimidazolyl, quinolyl, isoquinolyl, cinnolinyl, phtalazinyl, quinazolinyl,
20 quinoxalinyl, thiazolopyridinyl, oxazolopyridinyl and imidazo[2,1-*b*]thiazolyl;
wherein said heterocycles each independently may optionally be substituted
with one, or where possible, two or three substituents each independently
selected from Het², R¹¹ and C₁₋₄alkyl optionally substituted with one or two
substituents independently selected from Het² and R¹¹;
25 Het² represents a heterocycle selected from pyrrolyl, pyrrolinyl, imidazolyl,
imidazolinyl, pyrazolyl, pyrazolinyl, triazolyl, tetrazolyl, furanyl,
tetrahydrofuranyl, thienyl, thiolanyl, dioxolanyl, oxazolyl, oxazolinyl, isoxazolyl,
thiazolyl, thiazolinyl, isothiazolyl, thiadiazolyl, oxadiazolyl, pyridinyl, pyrimidinyl,
pyrazinyl, pyranyl, pyridazinyl, dioxanyl, dithianyl, trithianyl, triazinyl,
30 benzothienyl, isobenzothienyl, benzofuranyl, isobenzofuranyl, benzothiazolyl,
benzoxazolyl, indolyl, isoindolyl, indolinyl, purinyl, 1*H*-pyrazolo[3,4-*d*]pyrimidinyl, benzimidazolyl, quinolyl, isoquinolyl, cinnolinyl, phtalazinyl,

quinazolinyl, quinoxalinyl, thiazolopyridinyl, oxazolopyridinyl and imidazo[2,1-b]thiazolyl; wherein said heterocycles each independently may optionally be substituted with one, or where possible, two or three substituents each independently selected from R^{11} and C_{1-4} alkyl optionally substituted with one or two substituents independently selected from R^{11} ;

Het³ represents a monocyclic heterocycle selected from pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl, thiomorpholinyl and tetrahydropyranyl; wherein said monocyclic heterocycles each independently may optionally be substituted with, where possible, one, two, three or four substituents each independently selected from hydroxy, C_{1-4} alkyl, C_{1-4} alkyloxy, C_{1-4} alkylcarbonyl, piperidinyl, $NR^{12}R^{13}$, $C(=O)-Z-R^{14}$, R^6 and C_{1-4} alkyl substituted with one or two substituents independently selected from hydroxy, C_{1-4} alkyloxy, phenyl, $C(=O)-Z-R^{14}$, $-Y-C_{1-4}$ alkanediyl- $C(=O)-Z-R^{14}$, R^6 and $NR^{12}R^{13}$;

Het⁴ represents a monocyclic heterocycle selected from pyrrolyl, imidazolyl, pyrazolyl, triazolyl, tetrazolyl, furanyl, thienyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, thiadiazolyl, oxadiazolyl, pyridinyl, pyrimidinyl, pyrazinyl, pyranyl, pyridazinyl and triazinyl provided however that

- R^2 is other than C_{1-6} alkyloxycarbonyl- C_{1-6} alkyl, aminocarbonyl; and
- R^7 , R^8 , R^9 and R^{10} are other than aminocarbonyl, C_{1-4} alkylcarbonyloxy- C_{1-4} alkylcarbonyl, hydroxy C_{1-4} alkylcarbonyl, C_{1-4} alkyloxycarbonylcarbonyl $C(=O)-O-R^{14}$, C_{1-4} alkanediyl- $C(=O)-O-R^{14}$ and $-Y-C_{1-4}$ alkanediyl- $C(=O)-O-R^{14}$; and
- R^{12} and R^{13} are other than C_{1-4} alkylcarbonyloxy- C_{1-4} alkylcarbonyl, hydroxy C_{1-4} alkylcarbonyl, C_{1-4} alkylcarbonylcarbonyl; and
- R^{11} is other than $C(=O)-O-R^{14}$, $Y-C_{1-4}$ alkanediyl - $C(=O)-OR^{14}$, $C(=O)NH_2$, $C(=O)NHC_{1-4}$ alkyl or $C(=O)NHC_{3-7}$ cycloalkyl; and
- R^{14} is other than hydrogen, C_{1-4} alkyl, C_{3-7} cycloalkyl, aminocarbonylmethylene, mono- or di (C_{1-4} alkyl) aminocarbonylmethylene in the event Z is O; and
- R^{15} and R^{16} are other than aminocarbonyl, C_{1-4} alkylcarbonyloxy- C_{1-4} alkylcarbonyl, hydroxy C_{1-4} alkylcarbonyl or C_{1-4} alkyloxycarbonylcarbonyl; and

- Aryl is other than phenyl substituted with $C(=O)-O-R^{14}$ $C(=O)NH_2$, $C(=O)NHC_{1-4}alkyl$, $C(=O)NHC_{3-7}cycloalkyl$ and/or with $C_{1-4}alkyl$ substituted with $C(=O)-O-R^{14}$ or $Y-C_{1-4}alkanediyl - C(=O)-O-R^{14}$; and
- Het³ is other than a monocyclic heterocycle substituted with $C(=O)-O-R^{14}$ and/or with $C_{1-4}alkyl$ substituted with $C(=O)-O-R^{14}$ and/or $Y-C_{1-4}alkanediyl - C(=O)-O-R^{14}$; and
- The said compound of formula (I) contains at least one $-C(=O)-Z-R^{14}$ moiety.

An interesting group of compounds are those compounds of formula (I') wherein the 6-azauracil moiety is connected to the phenyl ring in the para or meta position relative to the carbon atom bearing the $-X-R^2$, R^3 and R^4 substituents; preferably in the para position.

Further compounds according to the invention include compounds of formula (I') wherein one or more of the following restrictions apply:

- p is 0, 1 or 2;
- X is S, NR^5 , or a direct bond; more in particular NH or a direct bond;
- each R^1 independently is halo, polyhalo $C_{1-6}alkyl$, $C_{1-6}alkyl$, $C_{1-6}alkyloxy$ or aryl, preferably, chloro or trifluoromethyl, more preferably chloro;
- R^2 is Het¹ or $C_{1-6}alkyl$ substituted with one or two substituents selected from hydroxy, cyano, amino, mono- or di($C_{1-4}alkyl$)amino, $C(=O)-Z-R^{14}$ $C_{1-6}alkyloxy$ optionally substituted with $C(=O)-Z-R^{14}$, $C_{1-6}alkylsulfonyloxy$, $C_{3-7}cycloalkyl$ optionally substituted with $C(=O)-Z-R^{14}$, aryl, aryloxy, arylthio, Het¹, Het¹oxy and Het¹thio; and if X is O, S or NR^5 , then R^2 may also represent aminothiocarbonyl, $C_{1-4}alkylcarbonyl$ optionally substituted with $C(=O)-Z-R^{14}$, $C_{1-4}alkylthiocarbonyl$ optionally substituted with $C(=O)-Z-R^{14}$, arylcarbonyl, arylthiocarbonyl, Het¹carbonyl or Het¹thiocarbonyl; particularly R^2 is Het¹ or in the event X is NH, R^2 may also be aminothiocarbonyl or Het¹carbonyl;
- R^3 is hydrogen, methyl, ethyl, propyl or cyclohexyl; preferably, methyl;
- R^4 is hydrogen or methyl; preferably, methyl;

- R³ and R⁴ are taken together to form a 1,4-butanediyl;
- R⁶ is C₁₋₆alkylsulfonyl or aminosulfonyl;
- R⁷ and R⁸ are each independently hydrogen, C₁₋₄alkyl, Het³ or R⁶;
- R⁹ and R¹⁰ are each independently hydrogen, C₁₋₄alkyloxyC₁₋₄alkyl,
5 C₁₋₄alkylcarbonyl, aminocarbonyl, Het³carbonyl, Het³ or R⁶;
- R¹¹ is cyano, nitro halo, C₁₋₄alkyloxy, formyl, NR⁷R⁸, C(=O)NR¹⁵R¹⁶,
-C(=O)-Z-R¹⁴, aryl, arylcarbonyl, Het³, Het⁴ and C(=O)Het³;
- R¹⁴ is dihydrofuranyl, C₅₋₂₀alkyl, C₁₋₄alkyl substituted with one or more
substituents selected from phenyl, C₁₋₄alkylamino, cyano, Het¹ and
10 C₃₋₇cycloalkyl;
- aryl is phenyl optionally substituted with one, two or three substituents each
independently selected from nitro, cyano, halo, hydroxy, C₁₋₄alkyl,
C₃₋₇cycloalkyl, C₁₋₄alkyloxy, formyl, polyhaloC₁₋₄alkyl, NR⁹R¹⁰,
C(=O)NR⁹R¹⁰, C(=O)-O-R¹⁴, -O-R⁶, phenyl, C(=O)Het³ and C₁₋₄alkyl
15 substituted with one or more substituents each independently selected from
halo, hydroxy, C₁₋₄alkyloxy, C(=O)-Z-R¹⁴, Het³ or NR⁹R¹⁰;
- Het¹ is a monocyclic heterocycle selected from pyrrolyl, imidazolyl, pyrazolyl,
triazolyl, tetrazolyl, furanyl, thienyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl,
thiadiazolyl, oxadiazolyl, pyridinyl, pyrimidinyl, pyrazinyl, pyranyl, pyridazinyl
20 and triazinyl, in particular imidazolyl, oxadiazolyl, thiazolyl, pyrimidinyl or
pyridinyl, wherein said monocyclic heterocycles each independently may
optionally be substituted with one, or where possible, two or three
substituents each independently selected from Het², R¹¹ and C₁₋₄alkyl
optionally substituted with Het² or R¹¹; preferably Het¹ is imidazolyl,
25 oxadiazolyl, thiazolyl or pyridinyl each independently and optionally
substituted with one, or where possible, two or three substituents each
independently selected from Het², R¹¹ and C₁₋₄alkyl optionally substituted
with Het² or R¹¹;
- Het² is an aromatic heterocycle; more in particular furanyl, thienyl, pyridinyl
30 or benzothienyl, wherein said aromatic heterocycles each independently

may optionally be substituted with one, or where possible, two or three substituents each independently selected from R^{11} and C_{1-4} alkyl;

- Het³ is piperidinyl, piperazinyl, morpholinyl and tetrahydropyranyl each independently and optionally substituted with, where possible, one, two, three or four substituents each independently selected from hydroxy, C_{1-4} alkyl, C_{1-4} alkylcarbonyl, piperidinyl and C_{1-4} alkyl substituted with one or two substituents independently selected from hydroxy, C_{1-4} alkyloxy and phenyl;
- Het⁴ is thienyl.

10 Special compounds are those compounds of formula (I') wherein p is 2 and both R^1 substituents are chloro; more preferably the two chloro substituents are in the ortho positions relative to the carbon atom bearing the $-X-R^2$, R^3 and R^4 substituents.

15 Particular compounds are those compounds of formula (I') wherein the 6-azauracil moiety is in the para position relative to the carbon atom bearing the $-X-R^2$, R^3 and R^4 substituents, and p is 2 whereby both R^1 substituents are chloro positioned ortho relative to the carbon atom bearing the $-X-R^2$, R^3 and R^4 substituents.

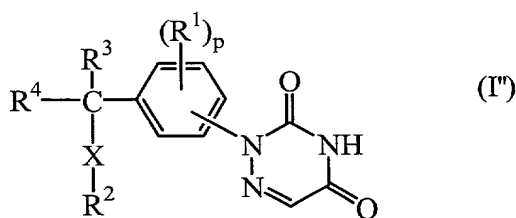
20 Other particular compounds are those compounds of formula (I') wherein X is a direct bond and R^2 is a monocyclic heterocycle selected from pyrrolyl, imidazolyl, pyrazolyl, triazolyl, tetrazolyl, furanyl, thienyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, thiadiazolyl, oxadiazolyl, pyridinyl, pyrimidinyl, pyrazinyl, 25 pyranyl, pyridazinyl and triazinyl, in particular imidazolyl, oxadiazolyl, thiazolyl, pyrimidinyl or pyridinyl, wherein said monocyclic heterocycles each independently may optionally be substituted with one, or where possible, two or three substituents each independently selected from Het², R^{11} and C_{1-4} alkyl optionally substituted with Het² or R^{11} ; more in particular R^2 is optionally 30 substituted thiazolyl, pyridinyl or oxadiazolyl.

Preferred compounds are those compounds of formula (I') wherein R^3 and R^4 are both methyl and $-X-R^2$ is Het^1 wherein Het^1 suitably is optionally substituted thiazolyl, pyridinyl or oxadiazolyl.

- 5 More preferred compounds are those compounds of formula (I') wherein R^3 and R^4 are both methyl, $-X-R^2$ is optionally substituted 2-thiazolyl or 3-oxadiazolyl, the 6-azauracil moiety is in the para position relative to the carbon atom bearing the $-X-R^2$, R^3 and R^4 substituents, and p is 2 whereby both R^1 substituents are chloro positioned ortho relative to the carbon atom bearing the $-X-R^2$, R^3 and R^4 substituents.

- 15 Examples of compounds of formula (I) further includes compounds of formula (I'') in which p, X, Y, R^1 , R^2 , R^3 , R^4 , R^5 , R^6 , R^7 , R^8 , R^9 , R^{10} , R^{11} , R^{12} , R^{13} , R^{14} , m, n, q, r, s R^a , R^b , R^c , R^d , R^e , R^f , R_g , R_h , R_k , R_i , R_j , R_m , R_n , R^{15} , R^{16} , R^{17} , R^{18} , Z, aryl, Het^1 , Het^2 , Het^3 , Het^4 , Het^5 as used in relation to compounds of formula (I'') have the meanings below:

The present invention is concerned with the compounds of formula



- 20 the *N*-oxides, the pharmaceutically acceptable addition salts and the stereochemically isomeric forms thereof, wherein :
- p represents an integer being 0, 1, 2, 3 or 4;
- X represents O, S, NR^5 or a direct bond or $-X-R^2$ taken together may represent cyano;
- 25 Y represents O, S, NR^5 , or $S(O)_2$;
- each R^1 independently represents $C(=O)-Z-R^{14}$, C_{1-6} alkyl, halo, polyhalo- C_{1-6} alkyl, hydroxy, mercapto, C_{1-6} alkyloxy, C_{1-6} alkylthio, C_{1-6} alkylcarbonyloxy, aryl, cyano, nitro, Het^3 , R^6 , NR^7R^8 or C_{1-4} alkyl substituted with $C(=O)-Z-R^{14}$,

Het³, R⁶ or NR⁷R⁸;

R² represents Het¹, C₃₋₇cycloalkyl optionally substituted with C(=O)-Z-R¹⁴,
C₁₋₆alkyl or C₁₋₆alkyl substituted with one or two substituents selected from
C(=O)-Z-R¹⁴, hydroxy, cyano, amino, mono- or di(C₁₋₄alkyl)amino,
5 C₁₋₆alkyloxy optionally substituted with C(=O)-Z-R¹⁴, C₁₋₆alkylsulfonyloxy,
C₃₋₇cycloalkyl optionally substituted with C(=O)-Z-R¹⁴, aryl, aryloxy, arylthio,
Het¹, Het¹oxy and Het¹thio; and if X is O, S or NR⁵, then R² may also
represent aminothiocarbonyl, C₁₋₄alkylcarbonyl optionally substituted with
C(=O)-Z-R¹⁴, C₁₋₄alkylthiocarbonyl optionally substituted with C(=O)-Z-R¹⁴,
10 arylcarbonyl, arylthiocarbonyl, Het¹carbonyl or Het¹thiocarbonyl;

R³ represents hydrogen, C₁₋₆alkyl or C₃₋₇cycloalkyl;

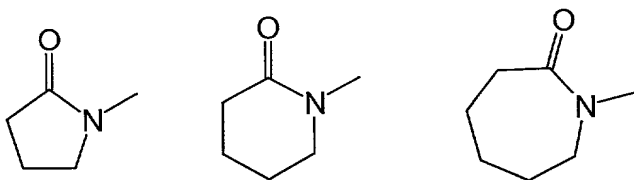
R⁴ represents hydrogen, C₁₋₆alkyl or C₃₋₇cycloalkyl; or

R³ and R⁴ taken together form a C₂₋₆alkanediyl;

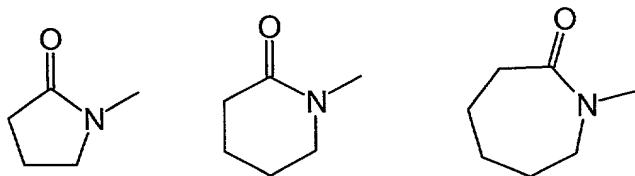
R⁵ represents hydrogen or C₁₋₄alkyl;

15 each R⁶ independently represents C₁₋₆alkylsulfonyl, aminosulfonyl,
piperidinylsulfonyl, mono- or di(C₁₋₄alkyl)aminosulfonyl, mono- or
di(benzyl)aminosulfonyl, polyhaloC₁₋₆alkylsulfonyl, C₁₋₆alkylsulfinyl,
phenylC₁₋₄alkylsulfonyl, piperazinylsulfonyl, aminopiperidinylsulfonyl,
piperidinylaminosulfonyl, *N*-C₁₋₄alkyl-*N*-piperidinylaminosulfonyl or mono-or
20 di(C₁₋₄alkyl)aminoC₁₋₄alkylsulfonyl;

each R⁷ and each R⁸ are independently selected from hydrogen, C₁₋₄alkyl,
hydroxyC₁₋₄alkyl, dihydroxyC₁₋₄alkyl, aryl, arylC₁₋₄alkyl, C₁₋₄alkyloxyC₁₋₄alkyl,
C₁₋₄alkylcarbonyl, arylcarbonyl, Het³carbonyl, mono- or di(C₁₋₄alkyl)aminoC₁₋₄
alkyl, arylaminocarbonyl, arylaminothiocarbonyl, Het³aminocarbonyl,
25 Het³aminothiocarbonyl, C₃₋₇cycloalkyl, pyridinylC₁₋₄alkyl, C₁₋₄alkanediyl-
C(=O)-Z-R¹⁴, -C(=O)-Z-R¹⁴, -Y-C₁₋₄alkanediyl-C(=O)-Z-R¹⁴, Het³, Het⁴ and
R⁶; or R⁷ and R⁸ taken together with the nitrogen atom to which they are
attached form a radical of formula



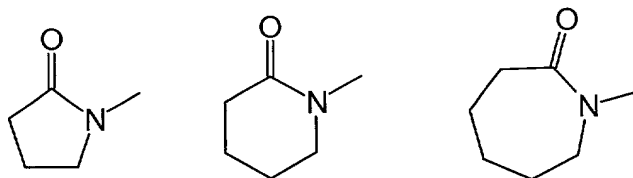
R^9 and R^{10} are each independently selected from hydrogen, C_{1-4} alkyl, hydroxy C_{1-4} alkyl, dihydroxy C_{1-4} alkyl, phenyl, phenyl C_{1-4} alkyl, C_{1-4} alkyloxy C_{1-4} alkyl, C_{1-4} alkylcarbonyl, phenylcarbonyl, Het³carbonyl, mono- or di(C_{1-4} alkyl)amino C_{1-4} alkyl, phenylaminocarbonyl, phenylaminothiocarbonyl, Het³aminocarbonyl, Het³aminothiocarbonyl, C_{3-7} cycloalkyl, pyridinyl C_{1-4} alkyl, C_{1-4} alkanediyl-C(=O)-Z- R^{14} , -C(=O)-Z- R^{14} , -Y- C_{1-4} alkanediyl-C(=O)-Z- R^{14} , Het³, Het⁴ and R^6 ; or R^9 and R^{10} taken together with the nitrogen atom to which they are attached form a radical of formula



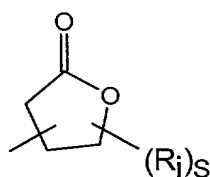
each R^{11} independently being selected from hydroxy, mercapto, cyano, nitro, halo, trihalomethyl, C_{1-4} alkyloxy optionally substituted with C(=O)-Z- R^{14} , formyl, trihalo C_{1-4} alkylsulfonyloxy, R^6 , NR^7R^8 , C(=O) $NR^{15}R^{16}$, -C(=O)-Z- R^{14} , -Y- C_{1-4} alkanediyl-C(=O)-Z- R^{14} , aryl, aryloxy, arylcarbonyl, C_{3-7} cycloalkyl optionally substituted with C(=O)-Z- R^{14} , C_{3-7} cycloalkyloxy optionally substituted with C(=O)-Z- R^{14} , phthalimide-2-yl, Het³ and C(=O)Het³;

R^{12} and R^{13} are each independently selected from hydrogen, C_{1-4} alkyl, hydroxy C_{1-4} alkyl, dihydroxy C_{1-4} alkyl, phenyl, phenyl C_{1-4} alkyl, C_{1-4} alkyloxy C_{1-4} alkyl, C_{1-4} alkylcarbonyl, phenylcarbonyl, mono- or di(C_{1-4} alkyl)amino C_{1-4} alkyl, phenylaminocarbonyl, phenylaminothiocarbonyl, C_{3-7} cycloalkyl, pyridinyl C_{1-4} alkyl, C_{1-4} alkanediyl-C(=O)-Z- R^{14} , -C(=O)-Z- R^{14} , -Y- C_{1-4} alkanediyl-C(=O)-Z- R^{14} and R^6 ; or R^{12} and R^{13} taken together with the

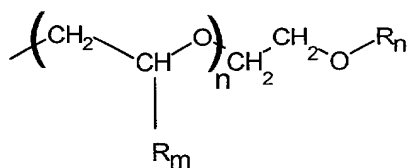
nitrogen atom to which they are attached form a radical of formula



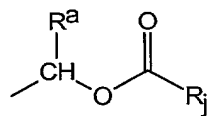
- each R^{14} independently represents hydrogen, C_{1-20} acyl (having a straight or
 5 branched, saturated or unsaturated hydrocarbon chain having 1 to 20
 carbon atoms), C_{1-20} alkyl, C_{3-20} alkenyl optionally substituted with phenyl,
 C_{3-20} alkynyl, C_{3-7} cycloalkyl, polyhalo C_{1-20} alkyl, Het⁵, phenyl or C_{1-20} alkyl
 substituted with one or more substituents selected from hydroxy, $NR^{17}R^{18}$,
 phenyl, mono- or di- $(C_{1-4}$ alkyl)amino, cyano, Het⁵, C_{1-4} alkyloxycarbonyl,
 10 phenyl C_{1-4} alkyloxycarbonyl and C_{3-7} cycloalkyl, or R^{14} represents a radical
 of formula



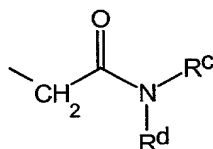
(a)



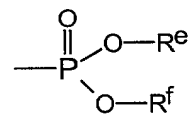
(b)



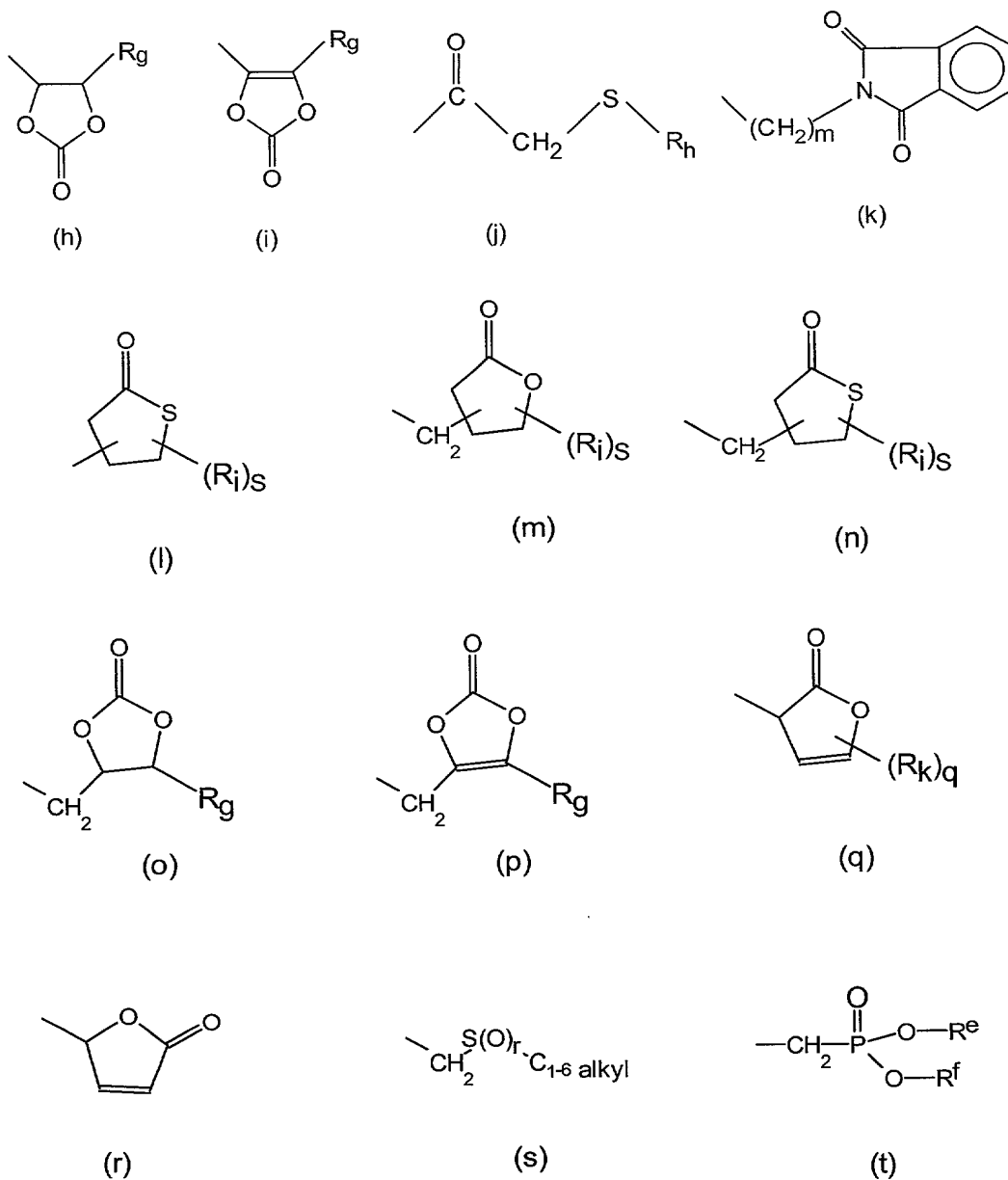
(c)



(d)



(e)



wherein m is 1 to 4, n is 0 to 5, q is 0 to 2, r is 0 to 2 and s is 0 to 4;

5 R^a , R^b , R^c , R^d , R^e and R^f are each independently hydrogen, C_{1-6} alkyl, phenyl or C_{3-7} cycloalkyl; or

R^e and R^f taken together may form $-CH_2-CH_2-$, $-CH_2-CH_2-CH_2-$ or $-CH_2-CH_2-CH_2-CH_2-$;

R_g , R_h and R_k are each independently hydrogen or C_{1-4} alkyl

R_i is C₁₋₄alkyl;

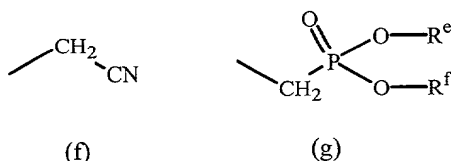
R_j is -O-R_b, C₁₋₆alkyl, phenyl or C₃₋₇cycloalkyl optionally substituted with C₁₋₄ alkyloxy;

where R_m is hydrogen or C₁₋₄ alkyloxy and R_n is hydrogen, C₁₋₄alkyl,

5 C₃₋₇cycloalkyl, phenyl or phenylC₁₋₄alkyl

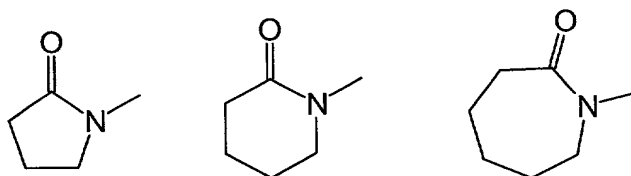
each Z independently represents O, S, NH, -CH₂-O- or -CH₂-S- whereby -CH₂- is attached to the carbonyl group; or

-Z-R¹⁴ taken together form a radical of formula



10 R¹⁵ and R¹⁶ are each independently selected from hydrogen, C₁₋₄alkyl, hydroxyC₁₋₄alkyl, dihydroxyC₁₋₄alkyl, aryl, arylC₁₋₄alkyl, C₁₋₄alkyloxyC₁₋₄alkyl, -C(=O)-Z-R¹⁴, arylcarbonyl, mono- or di(C₁₋₄alkyl)aminoC₁₋₄alkyl, arylaminocarbonyl, arylaminothiocarbonyl, aminocarbonylmethylene, mono- or di(C₁₋₄alkyl) aminocarbonylmethylene, Het³aminocarbonyl,

15 Het³aminothiocarbonyl, pyridinylC₁₋₄alkyl, Het³ or R⁶; or R¹⁵ and R¹⁶ taken together with the nitrogen atom to which they are attached form a radical of formula



R¹⁷ and R¹⁸ are each independently selected from hydrogen, C₁₋₄alkyl,

20 hydroxyC₁₋₄alkyl, dihydroxyC₁₋₄alkyl, phenyl, phenylC₁₋₄alkyl, C₁₋₄alkyloxyC₁₋₄alkyl, C₁₋₄alkylcarbonyl, phenylcarbonyl, mono- or di(C₁₋₄alkyl)aminoC₁₋₄alkyl, phenylaminocarbonyl, phenylaminothiocarbonyl, C₃₋₇cycloalkyl, pyridinylC₁₋₄alkyl, C₁₋₄alkanediyl-C(=O)-Z-C₁₋₆alkyl, -C(=O)-Z-C₁₋₆alkyl, -Y-C₁₋₄alkanediyl-C(=O)-Z-C₁₋₆alkyl and R⁶;

25 aryl represents phenyl optionally substituted with one, two or three substituents each independently selected from nitro, azido, cyano, halo, hydroxy,

C₁₋₄alkyl, C₃₋₇cycloalkyl, C₁₋₄alkyloxy, formyl, polyhaloC₁₋₄alkyl, NR⁹R¹⁰,
C(=O)NR⁹R¹⁰, C(=O)-Z-R¹⁴, R⁶, -O-R⁶, phenyl, Het³, C(=O)Het³ and C₁₋₄alkyl
substituted with one or more substituents each independently selected from
halo, hydroxy, C₁₋₄alkyloxy, C(=O)-Z-R¹⁴, -Y-C₁₋₄alkanediyl-C(=O)-Z-R¹⁴,
5 Het³ or NR⁹R¹⁰;

Het¹ represents a heterocycle selected from pyrrolyl, pyrrolinyl, imidazolyl,
imidazolinyl, pyrazolyl, pyrazolinyl, triazolyl, tetrazolyl, furanyl,
tetrahydrofuranyl, thienyl, thiolanyl, dioxolanyl, oxazolyl, oxazolinyl,
isoxazolyl, thiazolyl, thiazolinyl, isothiazolyl, thiadiazolyl, oxadiazolyl,
10 pyridinyl, pyrimidinyl, pyrazinyl, pyranyl, pyridazinyl, pyrrolidinyl, piperidinyl,
piperazinyl, morpholinyl, thiomorpholinyl, dioxanyl, dithianyl, trithianyl,
triazinyl, benzothienyl, isobenzothienyl, benzofuranyl, isobenzofuranyl,
benzothiazolyl, benzoxazolyl, benzodioxanyl, indolyl, isoindolyl, indolinyl,
purinyl, 1*H*-pyrazolo[3,4-*d*]pyrimidinyl, benzimidazolyl, quinolyl, isoquinolyl,
15 cinnolinyl, phtalazinyl, quinazolinyl, quinoxalinyl, thiazolopyridinyl,
oxazolopyridinyl and imidazo[2,1-*b*]thiazolyl; wherein said heterocycles each
independently may optionally be substituted with one, or where possible, two
or three substituents each independently selected from Het², R¹¹ and
C₁₋₄alkyl optionally substituted with one or two substituents independently
20 selected from Het² and R¹¹;

Het² represents a heterocycle selected from pyrrolyl, pyrrolinyl, imidazolyl,
imidazolinyl, pyrazolyl, pyrazolinyl, triazolyl, tetrazolyl, furanyl,
tetrahydrofuranyl, thienyl, thiolanyl, dioxolanyl, oxazolyl, oxazolinyl,
isoxazolyl, thiazolyl, thiazolinyl, isothiazolyl, thiadiazolyl, oxadiazolyl,
25 pyridinyl, pyrimidinyl, pyrazinyl, pyranyl, pyridazinyl, dioxanyl, dithianyl,
trithianyl, triazinyl, benzothienyl, isobenzothienyl, benzofuranyl, isobenzofuranyl,
benzothiazolyl, benzoxazolyl, indolyl, isoindolyl, indolinyl, purinyl,
1*H*-pyrazolo[3,4-*d*]pyrimidinyl, benzimidazolyl, quinolyl, isoquinolyl,
cinnolinyl, phtalazinyl, quinazolinyl, quinoxalinyl, thiazolopyridinyl,
30 oxazolopyridinyl and imidazo[2,1-*b*]thiazolyl; wherein said heterocycles each
independently may optionally be substituted with one, or where possible, two
or three substituents each independently selected from Het⁴, R¹¹ and C₁.

₄alkyl optionally substituted with one or two substituents independently selected from Het⁴ and R¹¹;

Het³ represents a monocyclic heterocycle selected from pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl, thiomorpholinyl and tetrahydropyranyl; wherein said
5 monocyclic heterocycles each independently may optionally be substituted with, where possible, one, two, three or four substituents each independently selected from hydroxy, C₁₋₄alkyl, C₁₋₄alkyloxy, C₁₋₄alkylcarbonyl, piperidinyl, NR¹²R¹³, C(=O)-Z-R¹⁴, R⁶ and C₁₋₄alkyl substituted with one or two substituents independently selected from hydroxy, C₁₋₄alkyloxy, phenyl,
10 C(=O)-Z-R¹⁴, -Y-C₁₋₄alkanediyl-C(=O)-Z-R¹⁴, R⁶ and NR¹²R¹³;

Het⁴ represents a monocyclic heterocycle selected from pyrrolyl, imidazolyl, pyrazolyl, triazolyl, tetrazolyl, furanyl, thienyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, thiadiazolyl, oxadiazolyl, pyridinyl, pyrimidinyl, pyrazinyl, pyranyl, pyridazinyl and triazinyl;

15 Het⁵ represents a heterocycle selected from pyrrolyl, pyrrolinyl, imidazolyl, imidazoliny, pyrazolyl, pyrazolinyl, triazolyl, tetrazolyl, furanyl, tetrahydrofuranyl, thienyl, thiolanyl, dioxolanyl, oxazolyl, oxazoliny, isoxazolyl, thiazolyl, thiazolinyl, isothiazolyl, thiadiazolyl, oxadiazolyl, pyridinyl, pyrimidinyl, pyrazinyl, pyranyl, pyridazinyl, pyrrolidinyl, piperidinyl,
20 piperazinyl, morpholinyl, thiomorpholinyl, tetrahydropyranyl, dioxanyl, dithianyl, trithianyl, triazinyl, benzothienyl, isobenzothienyl, benzofuranyl, isobenzofuranyl, benzothiazolyl, benzoxazolyl, benzodioxanyl, indolyl, isoindolyl, indoliny, purinyl, 1*H*-pyrazolo[3,4-*d*]pyrimidinyl, benzimidazolyl, quinolyl, isoquinolyl, cinnoliny, phtalazinyl, quinazolinyl, quinoxaliny, thiazolopyridinyl, oxazolopyridinyl and imidazo[2,1-*b*]thiazolyl; wherein said
25 heterocycles each independently may be substituted with, where possible, one, two, three or four substituents each independently selected from hydroxy, C₁₋₄alkyl, C₁₋₄alkyloxy, C₁₋₄alkylcarbonyl, piperidinyl, NR¹⁷R¹⁸, C(=O)-Z-C₁₋₆alkyl, R⁶, sulfonamido and C₁₋₄alkyl substituted with one or two substituents independently selected from hydroxy, C₁₋₄alkyloxy, phenyl,
30 C(=O)-Z-C₁₋₆alkyl, -Y-C₁₋₄alkanediyl-C(=O)-Z-C₁₋₆alkyl, R⁶ and NR¹⁷R¹⁸ ;

provided however that

- R^2 is other than C_{1-6} alkyloxycarbonyl C_{1-6} alkyl or aminocarbonyl; and
 - R^7 , R^8 , R^9 and R^{10} are other than aminocarbonyl, C_{1-4} alkylcarbonyloxy- C_{1-4} alkylcarbonyl, hydroxy C_{1-4} alkylcarbonyl, C_{1-4} alkyloxycarbonylcarbonyl, $C(=O)-O-R^{19}$, C_{1-4} alkanediyl $C(=O)-O-R^{19}$ or $-Y-C_{1-4}$ alkanediyl $C(=O)-O-R^{19}$; and
 - R^{12} and R^{13} are other than C_{1-4} alkylcarbonyloxy- C_{1-4} alkylcarbonyl, hydroxy C_{1-4} alkylcarbonyl or C_{1-4} alkylcarbonylcarbonyl; and
 - R^{11} is other than $C(=O)-O-R^{19}$, $Y-C_{1-4}$ alkanediyl – $C(=O)-OR^{19}$, $C(=O)NH_2$, $C(=O)NHC_{1-4}$ alkyl or $C(=O)NHC_{3-7}$ cycloalkyl; and
 - R^{15} and R^{16} are other than aminocarbonyl, C_{1-4} alkylcarbonyloxy- C_{1-4} alkylcarbonyl, hydroxy C_{1-4} alkylcarbonyl or C_{1-4} alkyloxycarbonylcarbonyl; and
 - aryl is other than phenyl substituted with $C(=O)-O-R^{19}$, $C(=O)NH_2$, $C(=O)NHC_{1-4}$ alkyl, $C(=O)NHC_{3-7}$ cycloalkyl and/or with C_{1-4} alkyl substituted with $C(=O)-O-R^{19}$ or $Y-C_{1-4}$ alkanediyl – $C(=O)-O-R^{14}$; and
 - Het^3 is other than a monocyclic heterocycle substituted with $C(=O)-O-R^{19}$ and/or with C_{1-4} alkyl substituted with $C(=O)-O-R^{19}$ and/or $Y-C_{1-4}$ alkanediyl – $(=O)-O-R^{19}$; and
 - in each of the above proviso's R^{19} is defined as hydrogen, C_{1-4} alkyl, C_{3-7} cycloalkyl, aminocarbonylmethylene or mono- or di(C_{1-4} alkyl)aminocarbonylmethylene; and
- the said compound of formula (I) contains at least one – $C(=O)-Z-R^{14}$ moiety.

An interesting group of compounds are those compounds of formula (I') wherein the 6-azauracil moiety is connected to the phenyl ring in the para or meta position relative to the carbon atom bearing the $-X-R^2$, R^3 and R^4 substituents; preferably in the para position. Another interesting group contains those compounds of formula (I') wherein one or more of the following restrictions apply :

- ♦ p is 0, 1 or 2;
- ♦ X is S, NR⁵ or a direct bond; more preferably a direct bond;
- ♦ each R¹ independently is halo, polyhaloC₁₋₆alkyl, C₁₋₆alkyl, C₁₋₆alkyloxy or aryl, preferably, chloro or trifluoromethyl, more preferably chloro;
- 5 ♦ the at least one – C(=O)-Z-R¹⁴ moiety contained by the compound of formula (I'') is born by R²,
- ♦ R² is Het¹ or C₁₋₆alkyl substituted with one or two substituents selected from hydroxy, cyano, amino, mono- or di(C₁₋₄alkyl)amino, C(=O)-Z-R¹⁴, C₁₋₆alkyloxy optionally substituted with C(=O)-Z-R¹⁴, C₁₋₆alkylsulfonyloxy, C₃₋₇cycloalkyl optionally substituted with C(=O)-Z-R¹⁴, aryl, aryloxy, arylthio, Het¹, Het¹oxy and Het¹thio; and if X is O, S or NR⁵, then R² may also represent aminothiocarbonyl, C₁₋₄alkylcarbonyl optionally substituted with C(=O)-Z-R¹⁴, C₁₋₄alkylthiocarbonyl optionally substituted with C(=O)-Z-R¹⁴, arylcarbonyl, arylthiocarbonyl, Het¹carbonyl or Het¹thiocarbonyl; more preferably R² is Het¹;
- 15 ♦ R³ is hydrogen, methyl, ethyl, propyl or cyclohexyl, more preferably methyl;
- ♦ R⁴ is hydrogen or methyl, more preferably methyl;
- ♦ R³ and R⁴ are taken together to form a 1,4-butanediyl;
- ♦ R⁶ is C₁₋₆alkylsulfonyl or aminosulfonyl;
- ♦ R⁷ and R⁸ are each independently hydrogen, C₁₋₄alkyl, Het³ or R⁶;
- 20 ♦ R⁹ and R¹⁰ are each independently hydrogen, C₁₋₄alkyloxyC₁₋₄alkyl, C₁₋₄alkylcarbonyl, aminocarbonyl, Het³carbonyl, Het³ or R⁶;
- ♦ R¹¹ is cyano, nitro, halo, C₁₋₄alkyloxy, formyl, NR⁷R⁸, C(=O)NR¹⁵R¹⁶, -C(=O)-Z-R¹⁴, aryl, arylcarbonyl, Het³ or C(=O)Het³; more preferably R¹¹ is phenyl, -C(=O)-O-R¹⁴,
- 25 -C(=O)-S-R¹⁴ or -C(=O)-NH-R¹⁴.
- ♦ R¹⁴ is dihydrofuranyl, C₅₋₂₀alkyl, C₃₋₂₀alkenyl, polyhaloC₁₋₆alkyl, Het⁵ or C₁₋₂₀alkyl substituted with one or more substituents selected from phenyl, C₁₋₄alkylamino, cyano, Het¹, hydroxy and C₃₋₇cycloalkyl;
- ♦ R¹⁷ and R¹⁸ are each independently hydrogen or phenyl;
- 30 ♦ aryl is phenyl optionally substituted with one, two or three substituents each independently selected from nitro, cyano, halo, hydroxy, C₁₋₄alkyl,

C₃₋₇cycloalkyl, C₁₋₄alkyloxy, formyl, polyhaloC₁₋₄alkyl, NR⁹R¹⁰, C(=O)NR⁹R¹⁰, C(=O)-O-R¹⁴, -O-R⁶, phenyl, C(=O)Het³ and C₁₋₄alkyl substituted with one or more substituents each independently selected from halo, hydroxy, C₁₋₄alkyloxy, C(=O)-Z-R¹⁴, Het³ and NR⁹R¹⁰;

- 5 ♦ Het¹ is a monocyclic heterocycle selected from pyrrolyl, imidazolyl, pyrazolyl, triazolyl, tetrazolyl, furanyl, thienyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, thiadiazolyl, oxadiazolyl, pyridinyl, pyrimidinyl, pyrazinyl, pyranal, pyridazinyl and triazinyl, in particular imidazolyl, oxadiazolyl, thiazolyl, pyrimidinyl or pyridinyl, wherein said monocyclic heterocycles each independently may
- 10 optionally be substituted with one, or where possible, two or three substituents each independently selected from Het², R¹¹ and C₁₋₄alkyl optionally substituted with Het² or R¹¹; more preferably Het¹ is imidazolyl, oxadiazolyl, thiazolyl or pyridinyl each independently and optionally substituted with one, or where possible, two or three substituents each independently selected from Het², R¹¹
- 15 and C₁₋₄alkyl optionally substituted with Het² or R¹¹;
- ♦ Het² is an aromatic heterocycle; more in particular furanyl, thienyl, pyridinyl or benzothienyl, wherein said aromatic heterocycles each independently may optionally be substituted with one, or where possible, two or three substituents each independently selected from R¹¹ and C₁₋₄alkyl;
- 20 ♦ Het³ is piperidinyl, piperazinyl, morpholinyl or tetrahydropyranyl each independently and optionally substituted with, where possible, one, two, three or four substituents each independently selected from hydroxy, C₁₋₄alkyl, C₁₋₄alkylcarbonyl, piperidinyl and C₁₋₄alkyl substituted with one or two substituents independently selected from hydroxy, C₁₋₄alkyloxy and phenyl;
- 25 ♦ Het⁴ is thienyl;
- ♦ Het⁵ is piperidinyl or piperazinyl optionally substituted with C₁₋₄alkyl or sulfonamido.

- Special compounds are those compounds of formula (I') wherein p is 2 and
- 30 both R¹ substituents are chloro; more preferably the two chloro substituents are in the ortho positions relative to the carbon atom bearing the -X-R², R³ and R⁴ substituents.

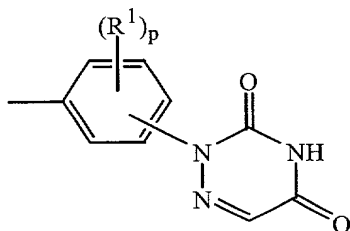
Particular compounds are those compounds of formula (I') wherein the 6-azauracil moiety is in the para position relative to the carbon atom bearing the -X-R², R³ and R⁴ substituents, and p is 2 whereby both R¹ substituents are
5 chloro positioned ortho relative to the carbon atom bearing the -X-R², R³ and R⁴ substituents.

Other particular compounds are those compounds of formula (I'') wherein X is a direct bond and R² is a monocyclic heterocycle selected from pyrrolyl,
10 imidazolyl, pyrazolyl, triazolyl, tetrazolyl, furanyl, thienyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, thiadiazolyl, oxadiazolyl, pyridinyl, pyrimidinyl, pyrazinyl, pyranal, pyridazinyl and triazinyl, in particular imidazolyl, oxadiazolyl, thiazolyl, pyrimidinyl or pyridinyl, wherein said monocyclic heterocycles each independently may optionally be substituted with one, or where possible, two or
15 three substituents each independently selected from Het², R¹¹ and C₁₋₄alkyl optionally substituted with Het² or R¹¹; more in particular R² is optionally substituted thiazolyl, pyridinyl or oxadiazolyl.

Preferred compounds are those compounds of formula (I'') wherein R³ and R⁴
20 are both methyl and -X-R² is Het¹ wherein Het¹ suitably is optionally substituted thiazolyl, pyridinyl or oxadiazolyl.

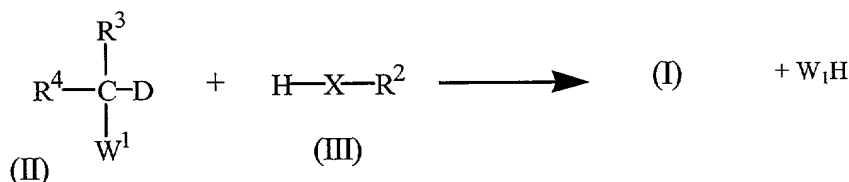
More preferred compounds are those compounds of formula (I'') wherein R³ and R⁴ are both methyl, -X-R² is optionally substituted 2-thiazolyl or 3-
25 oxadiazolyl, the 6-azauracil moiety is in the para position relative to the carbon atom bearing the -X-R², R³ and R⁴ substituents, and p is 2 whereby both R¹ substituents are chloro positioned ortho relative to the carbon atom bearing the -X-R², R³ and R⁴ substituents.

30 In order to simplify the structural representation of the compounds of formula (I), the group



will hereinafter be represented by the symbol D.

Compounds of formula (I) can generally be prepared by a series of reactions comprising the step of reacting an intermediate of formula (II) wherein W^1 is a suitable leaving group such as, for example, a halogen atom, with an appropriate reagent of formula (III).



Said reaction may be performed in a reaction-inert solvent such as, for example, acetonitrile, *N,N*-dimethylformamide, acetic acid, tetrahydrofuran, ethanol or a mixture thereof. Alternatively, in case the reagent of formula (III) acts as a solvent, no additional reaction-inert solvent is required. The reaction is optionally carried out in the presence of a base such as, for example, 1,8-diazabicyclo[5.4.0]undec-7-ene, sodium bicarbonate, sodium methanolate and the like. Convenient reaction temperatures range between -70°C and reflux temperature. In this and the following preparations, the reaction products may be isolated from the reaction medium and, if necessary, further purified according to methodologies generally known in the art such as, for example, extraction, crystallization, distillation, trituration and chromatography.

Some of the compounds and intermediates of the present invention can be prepared according to or analogous to the procedures described in EP-A-0,170,316, EP-A-0,232,932 and WO99/02505.

Alternatively, for instance, compounds of formula (I) may generally be prepared by cyclizing an intermediate of formula (IV) wherein L is a suitable leaving group such as, for example, C_{1-6} alkyloxy or halo, and E represents an appropriate electron attracting group such as, for example, an ester, an amide,

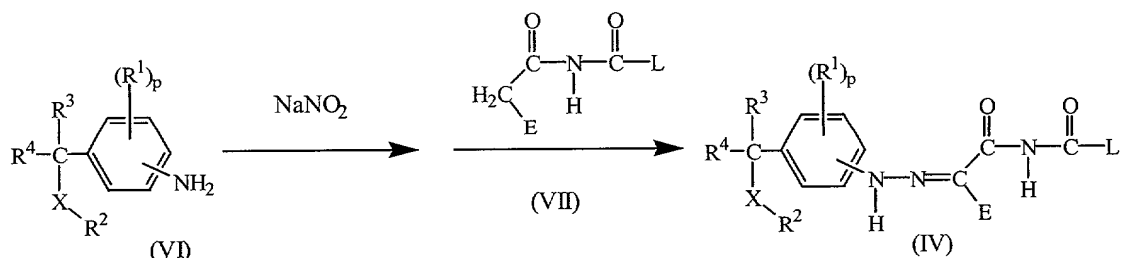
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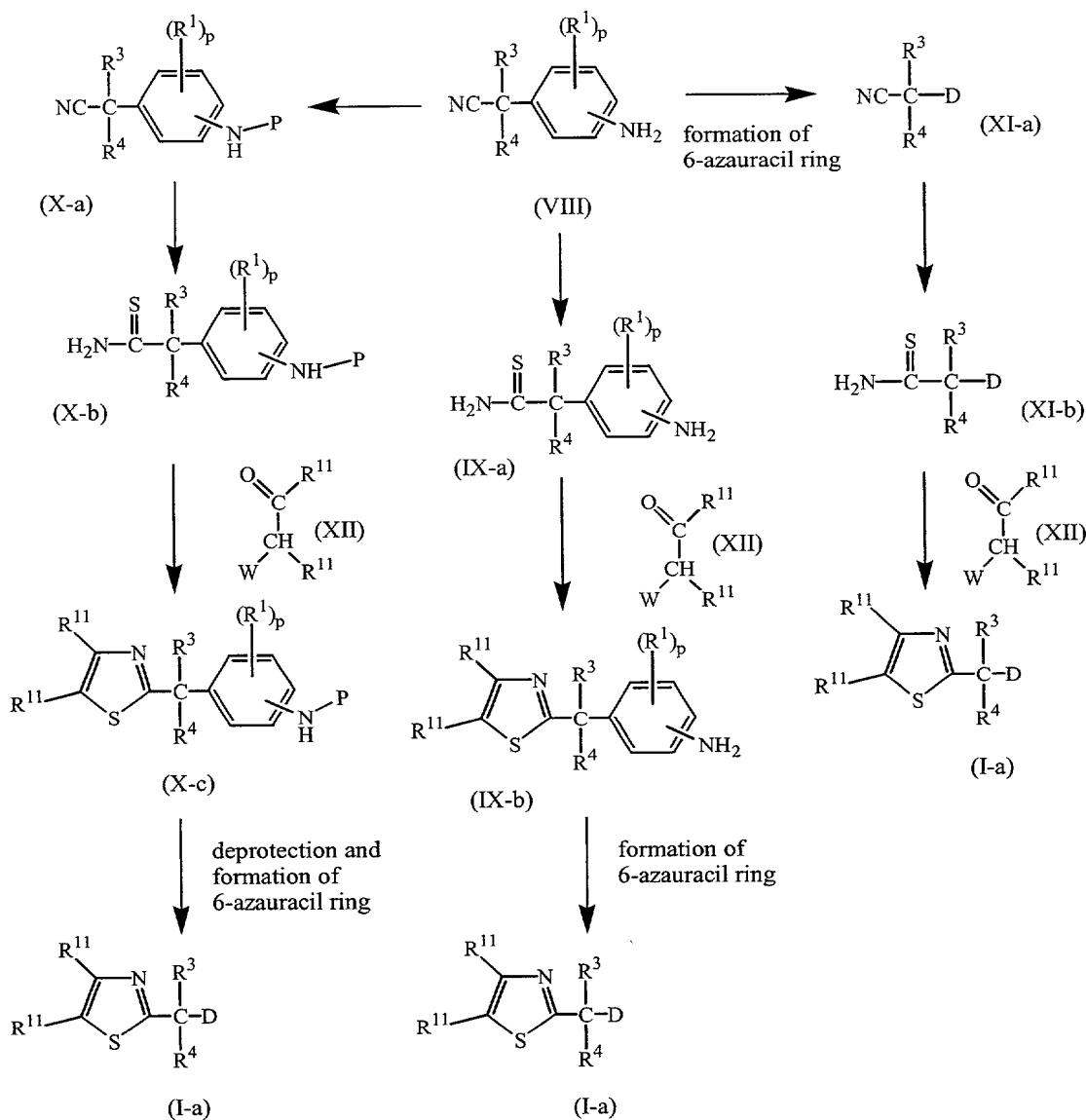
reaction of an intermediate of formula (VI) with sodium nitrate or a functional derivative thereof in an acidic medium such as for example hydrochloric acid in acetic acid, and preferably in the same reaction mixture, further reacting the thus obtained intermediate with a reagent of formula (VII) wherein L and E are as defined above, in the presence of a base such as, for example, sodium acetate.



An interesting subgroup within the present invention are those compounds of formula (I) wherein -X-R² is an optionally substituted 2-thiazolyl moiety, said compounds being represented by formula (I-a). The optionally substituted 2-thiazolyl moiety can be incorporated in the compounds of formula (I-a) at different stages of the preparation process.

For instance, scheme 1 above depicts three possible ways to prepare compounds of formula (I-a).

Scheme 1



A first pathway involves the reaction of the cyano moiety in an intermediate of formula (VIII) to the corresponding thioamide using H₂S gas in a suitable solvent such as, for example, pyridine and in the presence of a base such as, for example, triethylamine, thus obtaining an intermediate of formula (IX-a). This thioamide can then be cyclized with an intermediate of formula (XII) wherein W is a suitable leaving group such as, for example, a halogen, e.g. bromo, in a suitable solvent such as, for example, ethanol. The amino moiety in the resulting 2-thiazolyl derivative of formula (IX-b) can then be further reacted

as described hereinabove to form a 6-azauracil ring, thus obtaining a compound of formula (I-a).

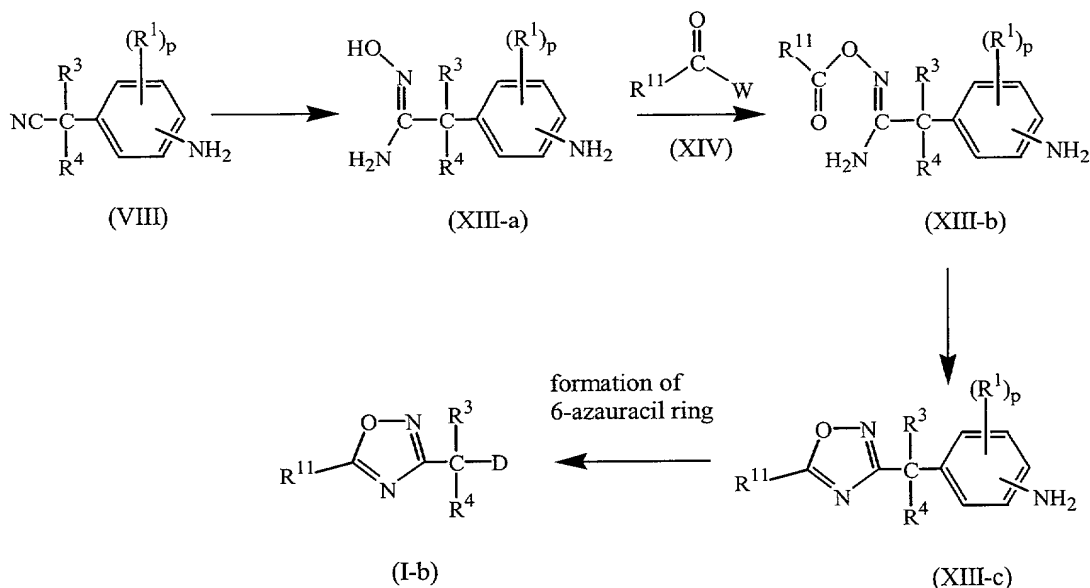
A second pathway to form compounds of formula (I-a) involves first the protecting of the amino moiety in an intermediate of formula (VIII) by
5 introducing a suitable protective group P such as, for example, an alkylcarbonyl group, using art-known protection techniques. In the example of P being a alkylcarbonyl group, the intermediates of formula (VII) can be reacted with the corresponding anhydride of formula $\text{alkyl-C(=O)-O-C(=O)-alkyl}$ in an appropriate solvent such as, for example, toluene. The thus obtained
10 intermediate of formula (X-a) can then be further reacted according to the first pathway described hereinabove. The final step, before formation of the 6-azauracil ring can be initiated after having deprotected the amino moiety using art-known deprotection techniques. In the example of P being a alkylcarbonyl group, the intermediates of formula (X-c) may be deprotected by reacting them
15 in a suitable solvent such as, for example, ethanol, in the presence of an acid such as, for example, hydrochloric acid.

A third pathway involves first the formation of the 6-azauracil ring as described hereinabove but starting from an intermediate of formula (VIII), and subsequently reacting the thus formed intermediate of formula (XI-a) with H_2S
20 and further reacting the thioamide of formula (XI-b) with an intermediate of formula (XII) as described in the first pathway, to finally form a compound of formula (I-a).

Another interesting subgroup within the present invention are those compounds of formula (I) wherein $-\text{X-R}^2$ is an optionally substituted 1,2,4-oxadiazol-3-yl moiety, said compounds being represented by formula (I-b-1).
25 The optionally substituted 1,2,4-oxadiazol-3-yl moiety can be incorporated at the same stages of the reaction procedure as depicted for the 2-thiazolyl derivatives in scheme 1.

For instance, analogous to one of the three pathways shown in scheme
30 1, compounds of formula (I-b-1) can be prepared by reacting an intermediate of formula (VIII) as depicted in scheme 2.

Scheme 2

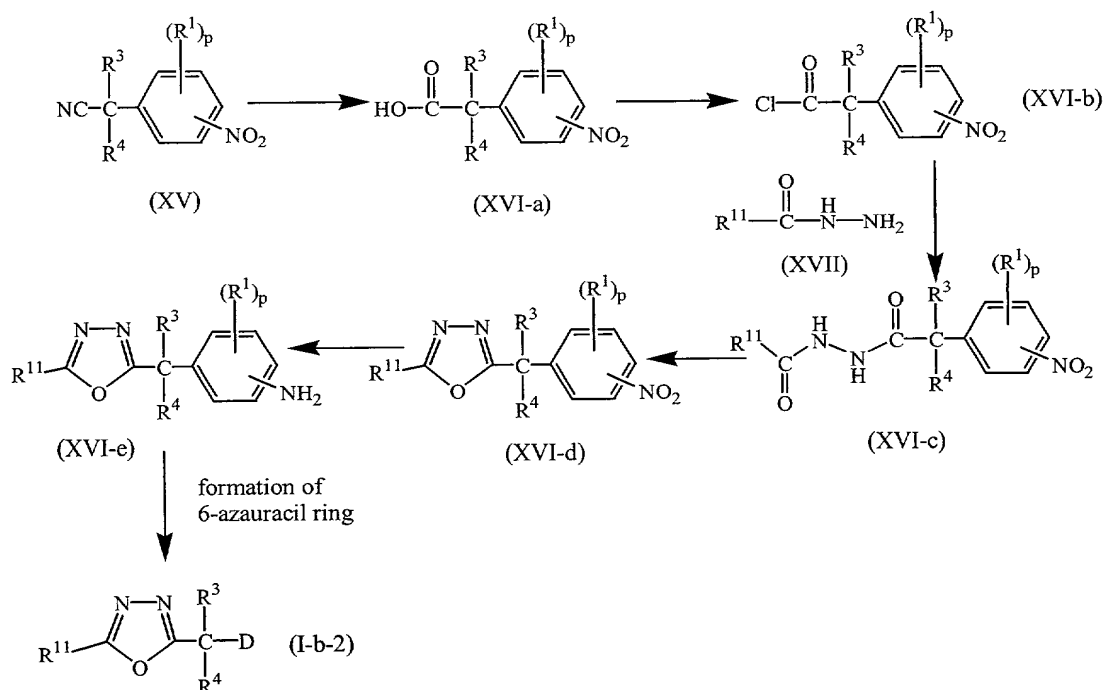


- In said scheme 2, the cyano group of an intermediate of formula (VIII) is reacted with hydroxylamine or a functional derivative thereof in a suitable solvent such as, for example, methanol, and in the presence of a base such as, for example sodium methanolate. The thus formed intermediate of formula (XIII-a) is then reacted with an intermediate of formula (XIV) wherein W is a suitable leaving group such as, for example, a halogen, e.g. chloro, in an appropriate solvent such as, for example, dichloromethane, and in the presence of a base, such as, for example, *N,N*-(1-methylethyl)ethaneamine.
- The resulting intermediate of formula (XIII-b) is then cyclized to a 3-oxadiazolyl derivative of formula (XIII-c). The amino moiety in the intermediates of formula (XIII-c) can then be transformed to the 6-azauracil ring as described above.

- Still another interesting subgroup within the present invention are those compounds of formula (I) wherein -X-R² is an optionally substituted 1,3,4-oxadiazol-2-yl moiety, said compounds being represented by formula (I-b-2).

For instance, compounds of formula (I-b-2) can be prepared as depicted in scheme 3.

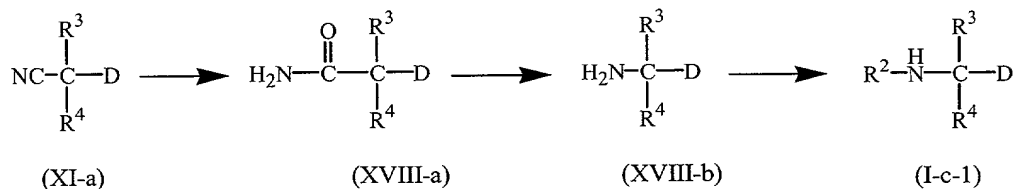
Scheme 3



- The nitrile moiety in an intermediate of formula (XV) is transformed into a carboxylic acid moiety using art-known techniques. For instance, the nitrile derivative may be refluxed in a mixture of sulfuric acid and acetic acid in water.
- The carboxylic acid derivative of formula (XVI-a) may the further be reacted with a chlorinating agent such as, for example, thionyl chloride, to form an acylchloride derivative of formula (XVI-b). Subsequently, The acyl chloride may be reacted with a hydrazine derivative of formula (XVII) in a suitable solvent such as, for example, dichloromethane, and in the presence of a base such as, for example *N,N*-(1-methylethyl)ethaneamine. The thus formed intermediate of formula (XVI-c) may be cyclized to a 1,2,4-oxadiazol-2-yl derivative of formula (XVI-d) in the presence of phosphoryl chloride. As a final step before the formation of the 6-azauracil ring as described above, the nitro group in the intermediates of formula (XVI-e) is reduced to an amino group using art-known reduction techniques such as, for instance, reducing the nitro group with hydrogen in methanol and in the presence of a catalyst such as Raney Nickel.

Yet another interesting subgroup within the present invention are those compounds of formula (I) wherein $-X-R^2$ is $-NH-R^2$, said compounds being represented by formula (I-c-1). Scheme 4 depicts a suitable pathway to obtain compounds of formula (I-c-1).

Scheme 4

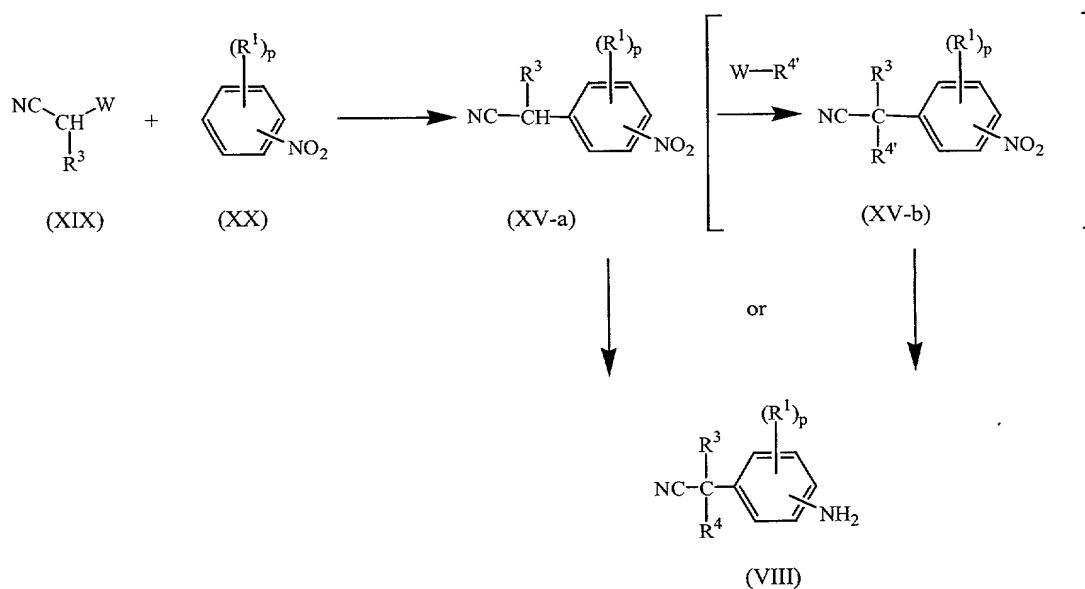


In said scheme 4, the cyano moiety of an intermediate of formula (XI-a) is hydrolized to the corresponding amide using art-known techniques such as, for instance, hydrolysis in the presence of acetic acid and sulfuric acid. The thus formed amide in the intermediates of formula (XVIII-a) can be transformed in an amine using (diacetoxyiodo)benzene or a functional derivative thereof in a suitable solvent such as, for example a mixture of water and acetonitrile. The amine derivative of formula (XVIII-b) can then be reacted with benzotriazol-1-yloxytris(dimethylamino) phosphonium hexafluoro-phosphate as described in Tetrahedron Letters No.14 (1975) p. 1219-1222 to obtain a compound, or with a functional derivative thereof such as, for instance, an isothiocyanate, in an appropriate solvent such as, for example, tetrahydrofuran.

Intermediates of formula (VIII) can be prepared as depicted in scheme 5.

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Scheme 5



An intermediate of formula (XIX) and an intermediate of formula (XX) may be reacted in a suitable solvent such as, for example, dimethylsulfoxide, in the presence of a base such as, for example sodium hydroxide, to form an intermediate of formula (XV-a). The nitro moiety in the intermediates of formula (XV-a) may either be immediately reduced to an amino group using art-known reduction techniques such as, for example, reducing the nitro group with hydrogen in methanol and in the presence of a catalyst such as Raney Nickel, or may first be reacted with an intermediate of formula $\text{R}^{4'}\text{-W}$ wherein $\text{R}^{4'}$ is the same as R^4 but other than hydrogen and W is a suitable leaving group such as, for example, a halogen, e.g. iodo, in a suitable solvent such as, for example, *N,N*-dimethylformamide, and in the presence of a suitable base such as, for example, sodium hydride, before reducing the nitro moiety.

The compounds of formula (I) can also be converted into each other following art-known procedures of functional group transformation such as, for example, those mentioned in WO99/02505 and the ones exemplified in the experimental part hereinafter. In particular, compounds of formula (I) containing at least one $-\text{C}(=\text{O})-\text{Z}-\text{R}^{14}$ moiety born by R^2 , wherein Z is O or S and R^{14} is other than hydrogen, can suitably be prepared by reacting the compound of formula (XXI) containing the corresponding moiety $-\text{C}(=\text{O})-\text{Z}-\text{H}$ with an

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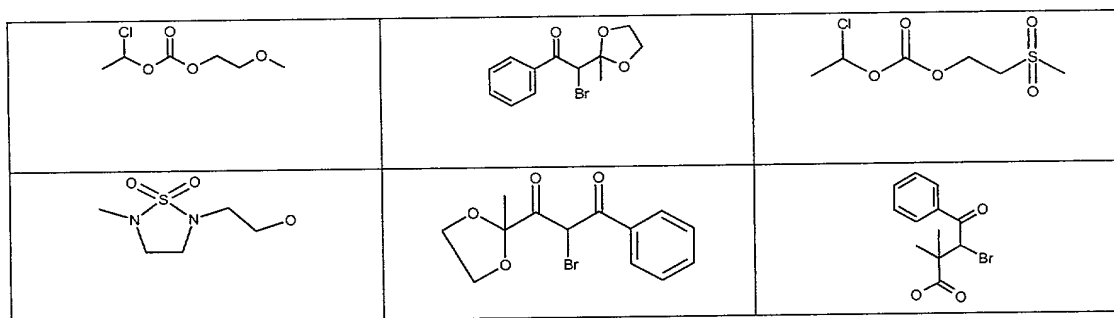
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wherein R²⁰ and R²¹ are each independently selected from hydrogen or C₁₋₂₀ alkyl or R²⁰ and R²¹ taken together with the carbon atom to which they are

attached form a cycloalkyl radical. These new compounds are useful for preparing a compound of formula (I) when Het⁵ represents a sulfonamido substituted piperazine. Such intermediate compounds of formula (XXIII) can be prepared by reacting N,N-dimethyl-1-piperazinesulfonamide with an alkylene oxide in a reaction-inert solvent such as methanol and/or methylene chloride. Suitable alkylene oxides for this purpose include for instance ethylene oxide, propylene oxide, 1-2 butylene oxide, cyclohexylene oxide and the like.

The present invention is also concerned with new compounds of formulae:



which are useful intermediates in the preparation of some of the compounds of formula (I).

The compounds of formula (I) may also be converted to the corresponding N-oxide forms following art-known procedures for converting a trivalent nitrogen into its N-oxide form. Said N-oxidation reaction may generally be carried out by reacting the starting material of formula (I) with 3-phenyl-2-(phenylsulfonyl)oxaziridine or with an appropriate organic or inorganic peroxide. Appropriate inorganic peroxides comprise, for example, hydrogen peroxide, alkali metal or earth alkaline metal peroxides, e.g. sodium peroxide, potassium peroxide; appropriate organic peroxides may comprise peroxy acids such as, for example, benzenecarboperoxoic acid or halo substituted benzenecarboperoxoic acid, e.g. 3-chlorobenzenecarboperoxoic acid, peroxyalkanoic acids, e.g. peroxyacetic acid, alkylhydroperoxides, e.g. t-butyl hydroperoxide. Suitable solvents are, for example, water, lower alkanols, e.g. ethanol and the like, hydrocarbons, e.g. toluene, ketones, e.g. 2-butanone,

halogenated hydrocarbons, e.g. dichloromethane, and mixtures of such solvents.

Pure stereochemically isomeric forms of the compounds of formula (I) may be obtained by the application of art-known procedures. Diastereomers
5 may be separated by physical methods such as selective crystallization and chromatographic techniques, e.g. counter-current distribution, liquid chromatography and the like.

Some of the compounds of formula (I) and some of the intermediates in the present invention may contain an asymmetric carbon atom. Pure
10 stereochemically isomeric forms of said compounds and said intermediates can be obtained by the application of art-known procedures. For example, diastereoisomers can be separated by physical methods such as selective crystallization or chromatographic techniques, e.g. counter current distribution, liquid chromatography and the like methods. Enantiomers can be obtained
15 from racemic mixtures by first converting said racemic mixtures with suitable resolving agents such as, for example, chiral acids, to mixtures of diastereomeric salts or compounds; then physically separating said mixtures of diastereomeric salts or compounds by, for example, selective crystallization or chromatographic techniques, e.g. liquid chromatography and the like methods;
20 and finally converting said separated diastereomeric salts or compounds into the corresponding enantiomers. Pure stereochemically isomeric forms may also be obtained from the pure stereochemically isomeric forms of the appropriate intermediates and starting materials, provided that the intervening reactions occur stereospecifically.

25 An alternative manner of separating the enantiomeric forms of the compounds of formula (I) and intermediates involves liquid chromatography, in particular liquid chromatography using a chiral stationary phase.

Some of the intermediates and starting materials as used in the reaction procedures mentioned hereinabove are known compounds and may be
30 commercially available or may be prepared according to art-known procedures.

IL-5, also known as eosinophil differentiating factor (EDF) or eosinophil colony stimulating factor (Eo-CSF), is a major survival and differentiation factor

for eosinophils and therefore thought to be a key player in eosinophil infiltration into tissues. There is ample evidence that eosinophil influx is an important pathogenic event in bronchial asthma and allergic diseases such as, cheilitis, irritable bowel disease, eczema, urticaria, vasculitis, vulvitis, winterfeet, atopic dermatitis, pollinosis, allergic rhinitis and allergic conjunctivitis; and other inflammatory diseases, such as eosinophilic syndrome, allergic angiitis, eosinophilic fasciitis, eosinophilic pneumonia, PIE syndrome, idiopathic eosinophilia, eosinophilic myalgia, Crohn's disease, ulcerative colitis and the like diseases.

The present compounds also inhibit the production of other chemokines such as monocyte chemotactic protein-1 and -3 (MCP-1 and MCP-3). MCP-1 is known to attract both T-cells, in which IL-5 production mainly occurs, and monocytes, which are known to act synergetically with eosinophils (Carr et al., 1994, Immunology, 91, 3652-3656). MCP-3 also plays a primary role in allergic inflammation as it is known to mobilize and activate basophil and eosinophil leukocytes (Baggiolini et al., 1994, Immunology Today, 15(3), 127-133).

The present compounds have no or little effect on the production of other chemokines such as IL-1, IL-2, IL-3, IL-4, IL-6, IL-10, γ -interferon (IFN- γ) and granulocyte-macrophage colony stimulating factor (GM-CSF) indicating that the present IL-5 inhibitors do not act as broad-spectrum immunosuppressives.

The selective chemokine inhibitory effect of the present compounds can be demonstrated by *in vitro* chemokine measurements in human blood. *In vivo* observations such as the inhibition of eosinophilia in mouse ear, the inhibition of blood eosinophilia in the *Ascaris* mouse model; the reduction of serum IL-5 protein production and splenic IL-5 mRNA expression induced by anti-CD3 antibody in mice and the inhibition of allergen- or Sephadex-induced pulmonary influx of eosinophils in guinea-pig are indicative for the usefulness of the present compounds in the treatment of eosinophil-dependent inflammatory diseases.

The present inhibitors of IL-5 production are particularly useful for administration via inhalation.

The intermediates of formula (XI-a) are interesting intermediates. Not only have they a particular usefulness as intermediates in the preparation of the compounds of formula (I), they also have valuable pharmacological activity.

In view of the above pharmacological properties, the compounds of formula (I) can be used as a medicine. In particular, the present compounds can be used in the manufacture of a medicament for treating eosinophil-dependent inflammatory diseases as mentioned hereinabove, more in particular bronchial asthma, atopic dermatitis, allergic rhinitis and allergic conjunctivitis.

In view of the utility of the compounds of formula (I), there is provided a method of treating warm-blooded animals, including humans, suffering from eosinophil-dependent inflammatory diseases, in particular bronchial asthma, atopic dermatitis, allergic rhinitis and allergic conjunctivitis. Said method comprises the systemic or topical administration of an effective amount of a compound of formula (I), a *N*-oxide form, a pharmaceutically acceptable addition salt or a possible stereoisomeric form thereof, to warm-blooded animals, including humans.

The present invention also provides compositions for treating eosinophil-dependent inflammatory diseases comprising a therapeutically effective amount of a compound of formula (I) and a pharmaceutically acceptable carrier or diluent.

To prepare the pharmaceutical compositions of this invention, a therapeutically effective amount of the particular compound, in base form or addition salt form, as the active ingredient is combined in intimate admixture with a pharmaceutically acceptable carrier, which may take a wide variety of forms depending on the form of preparation desired for administration. These pharmaceutical compositions are desirably in unitary dosage form suitable, preferably, for systemic administration such as parenteral administration; or topical administration such as via inhalation, a nose spray or the like. Application of said compositions may be by aerosol, e.g. with a propellant such as nitrogen, carbon dioxide, a freon, or without a propellant such as a pump spray, drops, lotions, or a semisolid such as a thickened composition which can

be applied by a swab. In particular, semisolid compositions such as salves, creams, gellies, ointments and the like will conveniently be used.

It is especially advantageous to formulate the aforementioned pharmaceutical compositions in dosage unit form for ease of administration and uniformity of dosage. Dosage unit form as used in the specification and claims herein refers to physically discrete units suitable as unitary dosages, each unit containing a predetermined quantity of active ingredient calculated to produce the desired therapeutic effect in association with the required pharmaceutical carrier. Examples of such dosage unit forms are tablets (including scored or coated tablets), capsules, pills, powder packets, wafers, injectable solutions or suspensions, teaspoonfuls, tablespoonfuls and the like, and segregated multiples thereof.

In order to enhance the solubility and/or the stability of the compounds of formula (I) in pharmaceutical compositions, it can be advantageous to employ α -, β - or γ -cyclodextrins or their derivatives. Also co-solvents such as alcohols may improve the solubility and/or the stability of the compounds of formula (I) in pharmaceutical compositions. In the preparation of aqueous compositions, addition salts of the subject compounds are obviously more suitable due to their increased water solubility.

Appropriate cyclodextrins are α -, β -, γ -cyclodextrins or ethers and mixed ethers thereof wherein one or more of the hydroxy groups of the anhydroglucose units of the cyclodextrin are substituted with C_{1-6} alkyl, particularly methyl, ethyl or isopropyl, e.g. randomly methylated β -CD; hydroxy C_{1-6} alkyl, particularly hydroxyethyl, hydroxy-propyl or hydroxybutyl; carboxy C_{1-6} alkyl, particularly carboxymethyl or carboxy-ethyl; C_{1-6} alkylcarbonyl, particularly acetyl; C_{1-6} alkyloxycarbonyl C_{1-6} alkyl or carboxy- C_{1-6} alkyloxy C_{1-6} alkyl, particularly carboxymethoxypropyl or carboxyethoxy-propyl; C_{1-6} alkylcarbonyloxy C_{1-6} alkyl, particularly 2-acetyloxypropyl. Especially noteworthy as complexants and/or solubilizers are β -CD, randomly methylated β -CD, 2,6-dimethyl- β -CD, 2-hydroxyethyl- β -CD, 2-hydroxyethyl- γ -CD, 2-hydroxypropyl- γ -CD and (2-carboxymethoxy)propyl- β -CD, and in particular 2-

hydroxypropyl- β -CD (2-HP- β -CD).

The term mixed ether denotes cyclodextrin derivatives wherein at least two cyclodextrin hydroxy groups are etherified with different groups such as, for example, hydroxypropyl and hydroxyethyl.

5 The average molar substitution (M.S.) is used as a measure of the average number of moles of alkoxy units per mole of anhydroglucose. The M.S. value can be determined by various analytical techniques, preferably, as measured by mass spectrometry, the M.S. ranges from 0.125 to 10.

10 The average substitution degree (D.S.) refers to the average number of substituted hydroxyls per anhydroglucose unit. The D.S. value can be determined by various analytical techniques, preferably, as measured by mass spectrometry, the D.S. ranges from 0.125 to 3.

15 Due to their high degree of selectivity as IL-5 inhibitors, the compounds of formula (I) as defined above, are also useful to mark or identify receptors. To this purpose, the compounds of the present invention need to be labelled, in particular by replacing, partially or completely, one or more atoms in the molecule by their radioactive isotopes. Examples of interesting labelled compounds are those compounds having at least one halo which is a radioactive isotope of iodine, bromine or fluorine; or those compounds having
20 at least one ^{11}C -atom or tritium atom.

One particular group consists of those compounds of formula (I) wherein R^1 is a radioactive halogen atom. In principle, any compound of formula (I) containing a halogen atom is prone for radiolabelling by replacing the halogen atom by a suitable isotope. Suitable halogen radioisotopes to this purpose are
25 radioactive iodides, e.g. ^{122}I , ^{123}I , ^{125}I , ^{131}I ; radioactive bromides, e.g. ^{75}Br , ^{76}Br , ^{77}Br and ^{82}Br , and radioactive fluorides, e.g. ^{18}F . The introduction of a radioactive halogen atom can be performed by a suitable exchange reaction or by using any one of the procedures as described hereinabove to prepare halogen derivatives of formula (I).

30 Another interesting form of radiolabelling is by substituting a carbon atom by a ^{11}C -atom or the substitution of a hydrogen atom by a tritium atom.

Hence, said radiolabelled compounds of formula (I) can be used in a process of specifically marking receptor sites in biological material. Said process comprises the steps of (a) radiolabelling a compound of formula (I), (b) administering this radiolabelled compound to biological material and subsequently (c) detecting the emissions from the radiolabelled compound.

The term biological material is meant to comprise every kind of material which has a biological origin. More in particular this term refers to tissue samples, plasma or body fluids but also to animals, specially warm-blooded animals, or parts of animals such as organs.

The radiolabelled compounds of formula (I) are also useful as agents for screening whether a test compound has the ability to occupy or bind to a particular receptor site. The degree to which a test compound will displace a compound of formula (I) from such a particular receptor site will show the test compound ability as either an agonist, an antagonist or a mixed agonist/antagonist of said receptor.

When used in *in vivo* assays, the radiolabelled compounds are administered in an appropriate composition to an animal and the location of said radiolabelled compounds is detected using imaging techniques, such as, for instance, Single Photon Emission Computerized Tomography (SPECT) or Positron Emission Tomography (PET) and the like. In this manner the distribution of the particular receptor sites throughout the body can be detected and organs containing said receptor sites can be visualized by the imaging techniques mentioned hereinabove. This process of imaging an organ by administering a radiolabelled compound of formula (I) and detecting the emissions from the radioactive compound also constitutes a part of the present invention.

In general, it is contemplated that a therapeutically effective daily amount would be from 0.01 mg/kg to 50 mg/kg body weight, in particular from 0.05 mg/kg to 10 mg/kg body weight. A method of treatment may also include administering the active ingredient on a regimen of between two or four intakes per day.

Experimental part

In the examples hereinafter, "DMSO" stands for dimethylsulfoxide, "RT" stands for room temperature, "DMF" stand for *N,N*-dimethylformamide, "EtOAc" stands for ethylacetate, "DIPE" stands for diisopropylether and "THF" stands for tetrahydrofuran.

5 A. Preparation of the intermediate compounds

Example A1

a) A mixture of 2-chloropropionitrile (0.2 mole) and 1,3-dichloro-5-nitrobenzene (0.2 mole) in DMSO (50 ml) was added dropwise at RT to a solution of NaOH (1 mole) in DMSO (150 ml) while the temperature was kept
10 below 30°C. The mixture was stirred at RT for 1 hour, then poured out on ice and acidified with HCl. The precipitate was filtered off, washed with H₂O and taken up in CH₂Cl₂. The organic solution was washed with H₂O, dried, filtered and the solvent was evaporated. The residue was purified by column chromatography over silica gel (eluent: CH₂Cl₂/cyclohexane 70/30). The pure
15 fractions were collected and the solvent was evaporated, yielding 19.5 g (40%) of (±)-2,6-dichloro-α-methyl-4-nitrobenzeneacetonitrile (intermediate 1).

b) NaH 80% (0.0918 mole) was added portionwise at 0°C under N₂ flow to a solution of intermediate (1) (0.0612 mole) in DMF (100 ml). The mixture was stirred at 0°C under N₂ flow for 1 hour. CH₃I (0.0918 mole) was added
20 dropwise at 0°C. The mixture was stirred at 50°C for 12 hours, then poured out on ice and extracted with EtOAc. The organic layer was separated, washed with H₂O, dried, filtered and the solvent was evaporated, yielding 17.1 g of 2,6-dichloro-α,α-dimethyl-4-nitrobenzeneacetonitrile (intermediate 2).

c) A mixture of intermediate (2) (0.066 mole) in CH₃OH (200 ml) was
25 hydrogenated at RT under a 3 bar pressure for 1 hour with Raney Nickel (15 g) as a catalyst. After uptake of H₂, the catalyst was filtered through celite, washed with CH₃OH and the filtrate was evaporated, yielding 17.1 g of 4-amino-2,6-dichloro-α,α-dimethylbenzeneacetonitrile (intermediate 3).

Example A2

30 a) A solution of NaNO₂ (0.36 mole) in H₂O (50 ml) was added to a solution of intermediate (3) (0.34 mole) in acetic acid (700 ml) and HCl (102 ml), stirred at 10°C. The reaction mixture was stirred for 80 minutes at 10°C. A

powdered mixture of sodium acetate (1.02 mole) and diethyl(1,3-dioxo-1,3-propanediyl)biscarbamate (0.374 mole) was added and the reaction mixture was stirred for 40 minutes. The reaction mixture was poured out onto crushed ice. The precipitate was filtered off, washed with water, taken up into CH₂Cl₂, and the layers were separated. The organic layer was dried, filtered and the solvent evaporated, yielding 138.5 g (84%) of diethyl N,N'-[2-[[3,5-dichloro-4-(1-cyano-1-methylethyl)phenyl]hydrazono]-1,3-dioxo-1,3-propanediyl]dicarbamate (intermediate 4).

b) A solution of intermediate (4) (0.28 mole) and potassium acetate (0.28 mole) in acetic acid (1000 ml) was stirred and refluxed for 3 hours. The reaction mixture containing ethyl [[2-[[3,5-dichloro-4-(1-cyano-1-methylethyl)phenyl]-2,3,4,5-tetrahydro-3,5-dioxo-1,2,4-triazin-6-yl]carbonyl] carbamate (intermediate 5) was used as such in the next step.

c) Intermediate (5) (crude reaction mixture) was treated with HCl 36% (0.84 mole). The reaction mixture was stirred and refluxed for 4 hours, then stirred at RT over the weekend. The reaction mixture was poured out onto crushed ice and this mixture was extracted with CH₂Cl₂. The separated organic layer was dried, filtered and the solvent evaporated, yielding 111.6 g of 2-[[3,5-dichloro-4-(1-cyano-1-methylethyl)phenyl]-2,3,4,5-tetrahydro-3,5-dioxo-1,2,4-triazine-6-carboxylic acid (intermediate 6).

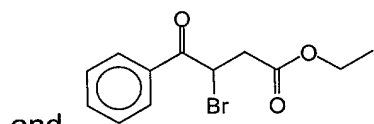
d) A suspension of intermediate (6) (0.28 mole) in mercaptoacetic acid (250 ml) was stirred for 4 hours at 100 °C, then allowed to cool to RT and stirred overnight. The reaction mixture was poured out onto crushed ice and this mixture was extracted with CH₂Cl₂. The separated organic layer was dried, filtered and the solvent evaporated. Toluene was added and azeotroped on the rotary evaporator. The residue was purified by short column chromatography over silica gel (eluent: CH₂Cl₂/CH₃OH 98/2). The pure fractions were collected and the solvent was evaporated. The residue was stirred in DIPE, filtered off, washed with DIPE, then dried, yielding 36.8 g (41%) of 2,6-dichloro-4-(4,5-dihydro-3,5-dioxo-1,2,4-triazin-2(3H)-yl)- α,α -dimethylbenzeneacetonitrile. The filtrate was stirred in DIPE and the resulting precipitate was filtered off, washed with DIPE, and dried, yielding 2.5 g (3%) of

2,6-dichloro-4-(4,5-dihydro-3,5-dioxo-1,2,4-triazin-2(3H)-yl)- α,α -dimethylbenzeneacetonitrile (intermediate 7).

e) A solution of intermediate (7) (0.107 mole) and *N,N*-bis(1-methylethyl)ethanamine (0.315 mole) in pyridine (500 ml) was stirred and heated to 80°C. H₂S was allowed to bubble through this solution for 24 hours at 80°C. H₂S gas inlet was stopped and the reaction mixture was stirred over the weekend at RT. The solvent was evaporated. 500 ml of a 9:1 CH₂Cl₂/CH₃OH mixture was added, and the resulting mixture was then poured out into 2 N HCl (1000 ml) at 0°C and stirred for 10 minutes. The precipitate was filtered off and dried, yielding 23.2 g (64%) of 2,6-dichloro-4-(4,5-dihydro-3,5-dioxo-1,2,4)- α,α -dimethylbenzeneethanethioamide (intermediate 8).

Example A3

Under a nitrogen atmosphere, a solution of intermediate (8) (0.0125 mole)



(0.0157 mole) in ethanol (60 ml) and DMF (30 ml; dried over molecular sieves) was stirred for 6.5 hours at 60 °C, then overnight at RT. The solvent was evaporated. The residue was taken up into water (100 ml) and this mixture was extracted with CH₂Cl₂ (100 ml). The separated organic layer was dried (MgSO₄), filtered and the solvent evaporated, then co-evaporated with toluene. The residue (13 g) was purified by flash column chromatography over silica gel (eluent: CH₂Cl₂/CH₃OH 100/0, then 99/1, ending with 98/2). The desired fractions were collected and the solvent was evaporated. Toluene was added and azeotroped on the rotary evaporator. The residue (6.5 g) was crystallized from CH₃CN. The precipitate was filtered off, washed with CH₃CN and DIPE, then dried under vacuum at 50°C, yielding 3.17 g (46.5 %) of ethyl-2-[1-[2,6-dichloro-4-(4,5-dihydro-3,5-dioxo-1,2,4-triazin-2(3H)-yl)]phenyl]-1-methylethyl]-4-phenyl-5-thiazoleacetate (intermediate 9) having a melting point of 148°C.

Example A4

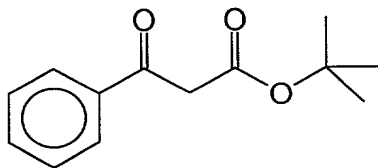
A mixture of intermediate (9) (0.00183 mole) and NaOH 1N (0.0055

mole) in CH₃OH (25 ml) and THF (25 ml) was stirred overnight at RT. The reaction mixture was acidified with 1N HCl (8 ml) and the resulting product was taken up into EtOAc. The organic layer was washed with brine, dried, filtered and the solvent was evaporated. The residue was crystallized from CH₃CN.

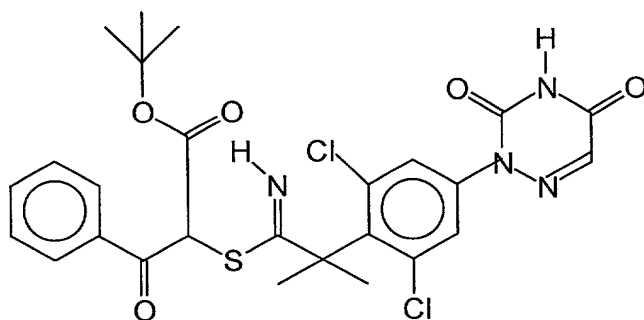
- 5 The precipitate was filtered off, washed with DIPE, and dried, yielding 0.8 g (79%) of 2-[1-[2,6-dichloro-4-(4,5-dihydro-3,5-dioxo-1,2,4-triazin-2(3H)yl)phenyl]-1-methylethyl]-4-phenyl-5-thiazoleacetic acid (intermediate 10).

Example A5

- 10 First a solution of bromine (0.02 mole) in CH₂Cl₂ (20 ml) was added dropwise at 10°C under a nitrogen flow to a mixture of a compound having the formula:

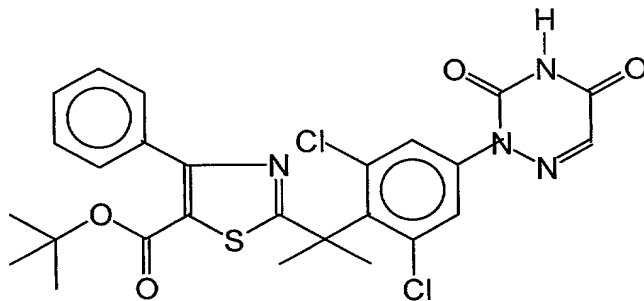


- (0.0227 mole) in CH₂Cl₂ (50ml). The mixture was stirred at 10°C for 1 hour.
- 15 H₂O and solid K₂CO₃ were added. The organic layer was separated, dried (MgSO₄), filtered and the solvent was evaporated. The reaction was carried out 4 times, using the same quantities and combining the residues, yielding 14 g (51%) of 1,1-dimethylethyl 3-bromo-3-oxo-benzenepropanoate. A mixture of intermediate (8) (0.0119 mole), 1,1-dimethylethyl 3-bromo-3-oxo-benzenepropanoate (0.0137 mole) and K₂CO₃ (0.0357 mole) in CH₃CN (55 ml)
- 20 was stirred at room temperature for 3.5 hours. Ice and EtOAc were added. The mixture was acidified with HCl 3N. The organic layer was separated, dried (MgSO₄), filtered and the solvent was evaporated. The product was used without further purification, yielding 8g of intermediate 11 having the formula



Example A6

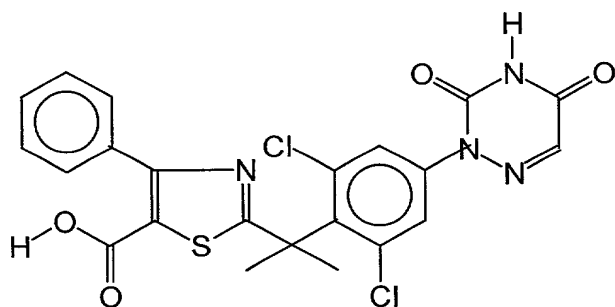
Intermediate (11) (0.0119 mole) and tert.-butanol (24 g) were stirred and refluxed for 2 hours. The mixture was brought to room temperature. The solvent was evaporated. The residue was taken up in CH_2Cl_2 . The organic solution was washed with H_2O , dried (MgSO_4), filtered and the solvent was evaporated. The residue (7.8g) was purified by column chromatography over silica gel (eluent: $\text{CH}_2\text{Cl}_2/\text{CH}_3\text{OH}$ 99/1; 15-40 μm). Two fractions were collected and their solvents were evaporated, yielding 2.66 g (fraction 1) and 0.7 g (fraction 2) respectively. Fraction 2 was purified by column chromatography (eluent: $\text{CH}_3\text{OH}/\text{NH}_4\text{OAc}$ 0.5% 80/20; column: HYPERSIL C18, 3 μm). The pure fractions were collected and the solvent was evaporated, yielding 0.45 g of intermediate 12 having a melting point of 130°C and represented by the formula



Example A7

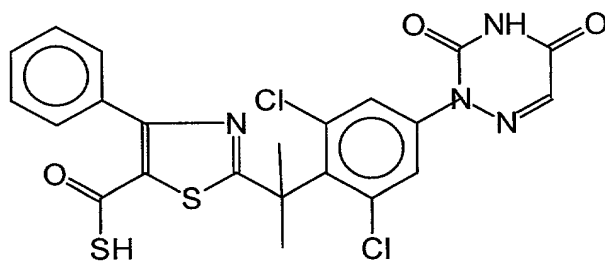
Intermediate 12 (0.00465 mole) was added portionwise at 0°C - 10°C to trifluoroacetic acid (35 ml). The mixture was stirred at room temperature for 3 hours and poured out into H_2O . The precipitate was filtered off, washed with H_2O and taken up in CH_2Cl_2 . The organic layer was separated, dried (MgSO_4),

filtered and the solvent was evaporated. The residue (2.4 g) was purified by column chromatography over silica gel (eluent: CH₂Cl₂/CH₃OH/NH₄OH 97/3/0.2; 15-40 μm). The pure fractions were collected and the solvent was evaporated. The residue was crystallized from CH₃CN. The precipitate was
 5 filtered off and dried, yielding 1.16 g of intermediate 13 having a melting point of 232°C and represented by the formula



Example A8

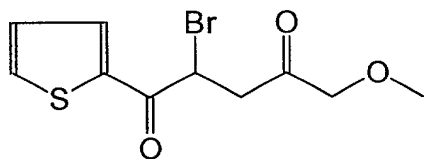
1,1'-carbonylbis-1H-imidazole (0.0159 mole) was added portionwise at
 10 RT under a nitrogen flow to a solution of intermediate (13) (0.00795 mole) in DMF (60 ml). The mixture was stirred at RT overnight. H₂S was bubbled through the mixture for 1 hour. The mixture was stirred at RT for 1 hour, poured out into a saturated NaCl solution and extracted twice with CH₂Cl₂. The combined organic layer was dried (MgSO₄), filtered and the solvent was
 15 evaporated. The resulting intermediate 14, represented by the formula



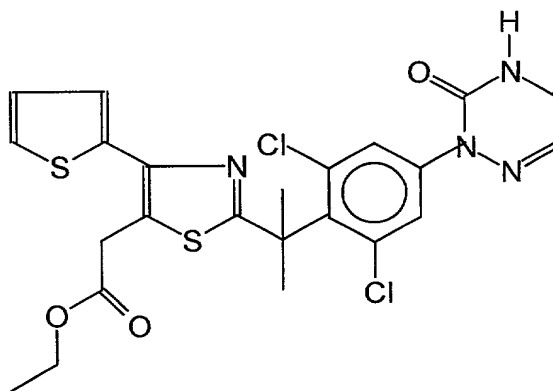
was used without further purification.

Example A9

A mixture of intermediate (8) (0.0158 mole) and



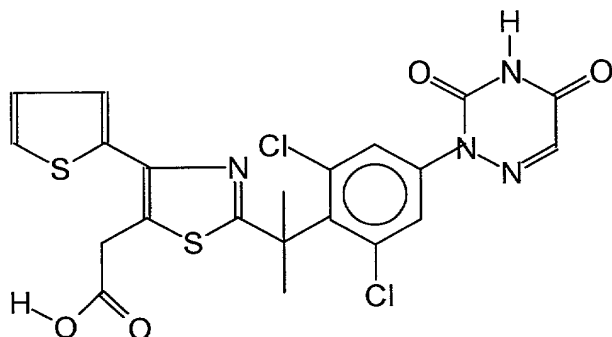
(0.0237 mole) in ethanol (60 ml) and DMF (40 ml) was stirred at 60°C for 4 hours. The solvent was evaporated. EtOAc was added. The organic solution was washed 3 times with H₂O, dried (MgSO₄), filtered and the solvent was evaporated. The residue (11.2 g) was purified by column chromatography over silica gel (eluent: CH₂Cl₂/CH₃OH 98/2; 15-40 μm). The desired fractions were collected and the solvent was evaporated, yielding 4.2 g (47%) of a product, part of which (1.5 g) was crystallized from petroleum ether and DIPE. The precipitate was filtered off and dried, yielding 1.15g of intermediate 15 having a melting point of 126°C and represented by the formula



Example A10

A mixture of intermediate (15) (0.0045 mole) and NaOH (0.0135 mole) in methanol (30 ml) and THF (30 ml) was stirred at room temperature for 12 hours, poured out on ice, acidified with HCl and extracted with EtOAc. The organic layer was separated, dried (MgSO₄), filtered and the solvent was evaporated. The residue (2.2 g) was purified by column chromatography over silica gel (eluent: CH₂Cl₂/CH₃OH/NH₄OH 95/5/0.1; 15-40 μm). The pure fractions were collected and the solvent was evaporated, yielding 1.5 g (64%)

of a product, part of which (1 g) was crystallized from diethyl ether. The precipitate was filtered off and dried, yielding 0.5 g of intermediate 16 having a melting point of 192°C and represented by the formula



5 Example A11

a) NaOCH₃ 30% (0.592 mole) was added to a solution of hydroxylamine hydrochloride (0.1085 mole) in CH₃OH (200 ml), stirred at RT. The mixture was stirred for 10 minutes. Intermediate (3) (0.0542 mole) was added portionwise and the resulting reaction mixture was stirred and refluxed overnight. The solvent was evaporated. The residue was partitioned between CH₂Cl₂ and water. The organic layer was separated, dried, filtered and the solvent was evaporated. The residue was stirred in DIPE, filtered off, washed with DIPE, and dried, yielding 3.7 g (26%) of 4-amino-2,6-dichloro-N'-hydroxy- α,α -dimethylbenzeneethanimidamide (intermediate 17).

b) A solution of intermediate (17) (0.0323 mole) and N,N-bis(methylethyl)ethanamine (0.0339 mole) in CH₂Cl₂ (190 ml) was stirred at 15°C. A solution of 2-methylbenzoyl chloride (0.0323 mole) in CH₂Cl₂ (10 ml) was added dropwise and the resulting reaction mixture was stirred for one hour. Water was added. The organic layer was separated, dried, filtered and the solvent was evaporated. Toluene was added and azeotroped on the rotary evaporator, yielding 13.0 g of [1-amino-2-(4-amino-2,6-dichlorophenyl)-2-methylpropylidene]amino 2-methylbenzoate (intermediate 18).

c) A solution of intermediate (18) (0.0323 mole) and paratoluenesulfonic acid (0.0323 mole) in DMSO (100 ml) was stirred for 30 minutes at 150°C. The reaction mixture was cooled. Water was added and this mixture was extracted

with toluene. The separated organic layer was dried, filtered and the solvent evaporated. The residue was purified by short column chromatography over silica gel (eluent: CH₂Cl₂). The desired fractions were collected and the solvent was evaporated. The concentrate was co-evaporated with EtOAc, yielding
5 11.7 g of 3,5-dichloro-4-[1-[5-(2-methylphenyl)-1,2,4-oxadiazol-3-yl]-1-methylethyl] benzenamine (intermediate 19).

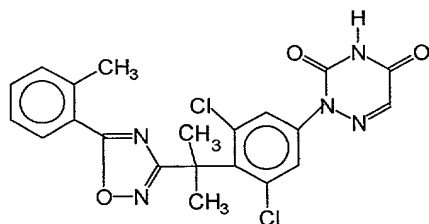
d) A solution of intermediate (19) (0.0302 mole) and concentrated HCl (0.0906 mole) in acetic acid (100 ml) was stirred at 0°C. A solution of NaNO₂ (0.032 mole) in water (10 ml) was added dropwise at 0°C. The reaction
10 mixture was stirred for 1 hour at 0°C. A powdered mixture of sodium acetate (0.0906 mole) and diethyl(1,3-dioxo-1,3-propanediyl)biscarbamate (0.0332 mole) was added portionwise. The mixture was allowed to warm to RT and stirred for 1 hour. Water was added and this mixture was extracted with CH₂Cl₂. The separated organic layer was dried, filtered and the solvent
15 evaporated, yielding diethyl N,N'-[2-[[3,5-dichloro-4-[1-[5-(2-methylphenyl)-1,2,4-oxadiazol-3-yl]-1-methylethyl]phenyl]hydrazono]-1,3-dioxo-1,3-propanediyl]dicarbamate (intermediate 20).

e) A solution of intermediate (20) (0.0302 mole) and sodium acetate (0.0302 mole) in acetic acid (200 ml) was stirred and refluxed for 3 hours. The
20 reaction mixture was poured out into water and this mixture was extracted with CH₂Cl₂. The separated organic layer was dried, filtered and the solvent evaporated. Toluene was added and azeotroped on the rotary evaporator, yielding ethyl [[2-[3,5-dichloro-4-[1-[5-(2-methylphenyl)-1,2,4-oxadiazol-3-yl]-1-methylethyl]phenyl]-2,3,4,5-tetrahydro-3,5-dioxo-1,2,4-triazin-6-yl]carbonyl]
25 carbamate (intermediate 21).

f) A mixture of intermediate (21) (0.0302 mole) in HCl 36% (10 ml) and acetic acid (200 ml) was stirred and refluxed overnight. The reaction mixture was poured out onto crushed ice and this mixture was extracted with CH₂Cl₂. The separated organic layer was dried, filtered and the solvent evaporated,
30 yielding 16.3 g of 2-[3,5-dichloro-4-[1-[5-[2-methylphenyl)-1,2,4-oxadiazol-3-yl]-1-methylethyl]phenyl]-2,3,4,5-tetrahydro-3,5-dioxo-1,2,4-triazine-6-carboxylic acid (intermediate 22).

Example A12

A mixture of intermediate (22) (0.0133 mole) in mercaptoacetic acid (7 ml) was stirred at 175°C for 2 hours. The mixture was cooled, poured out into ice water, basified with K₂CO₃ and extracted with EtOAc. The organic layer was separated, washed with H₂O, dried, filtered and the solvent was evaporated. The residue was purified by column chromatography over silica gel (eluent: CH₂Cl₂/CH₃OH 99/1). The pure fractions were collected and the solvent was evaporated, yielding 2.2 g (36%) of intermediate 23 represented by the formula

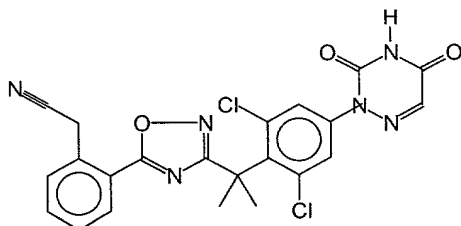


Example A13

A mixture of intermediate (23) (0.0011 mole), 1-bromo-2,5-pyrrolinedione (0.0011 mole) and dibenzoyl peroxide (catalytic quantity) in CCl₄ (30 ml) was stirred and refluxed for 3 hours. The mixture was allowed to cool to RT. The mixture was filtered over a diatomaceous earth commercially available under the tradename Dicalite and the filtrate contained 2-[4-[1-[5-[2-(bromomethyl)phenyl]-1,2,4-oxadiazol-3-yl]-1-methylethyl]-3,5-dichlorophenyl]-1,2,4-triazine-3,5(2*H*,4*H*)-dione (intermediate 24).

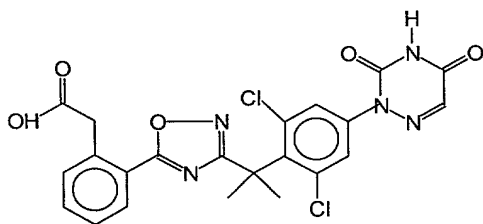
Example A14

A solution of intermediate (24) (0.017 mole) and KCN (0.034 mole) in ethanol (100 ml) and H₂O (30 ml) was stirred for 8 hours at 60°C. The solvent was evaporated under reduced pressure. The residue was taken up into CH₂Cl₂, then washed with water, dried (MgSO₄), filtered and the solvent was evaporated, yielding 8.2 g of intermediate 25 represented by the formula



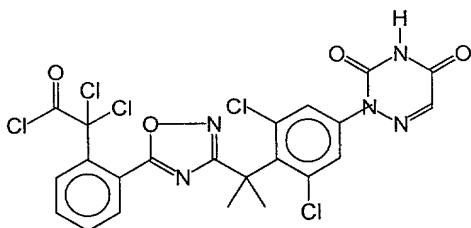
Example A15

A solution of intermediate (25) (0.017 mole) in HOAc (50 ml), H₂SO₄ (50 ml) and H₂O (50 ml) was stirred and refluxed for 2 hours. The reaction mixture was poured out into iced water and the resulting precipitate was filtered off, washed, then dissolved in CH₂Cl₂. The organic solution was dried, filtered and the solvent was evaporated. The residue was purified over silica gel on a glass filter (eluent: CH₂Cl₂/CH₃OH 95/5). The desired fractions were collected and the solvent was evaporated. The residue was purified by high performance liquid chromatography over RP BDS Hyperprep C18 (100 Å, 8 µm; gradient elution with (0.5% NH₄OAc in water/CH₃CN 90/10)/CH₃OH/CH₃CN). The pure fractions were collected and the solvent was evaporated. The residue was stirred in hexane, filtered off and dried under vacuum at 60°C, yielding 0.084 g of intermediate 26 represented by the formula



Example A16

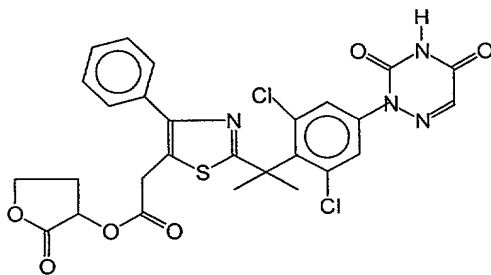
A solution of intermediate (26) (0.0014 mole) in SOCl₂ (15 ml) was stirred and refluxed for 1 hour. SOCl₂ was evaporated under reduced pressure. Toluene was added and azeotroped on the rotary evaporator, yielding 100% of intermediate 27 represented by the formula



B. Preparation of the final compounds

Example B1

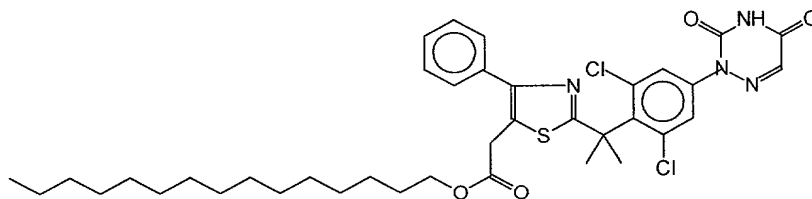
- 5 A mixture of 3-bromodihydro-2(3H)-furanone (0.0081 mole) in DMF (16ml) was added dropwise at room temperature to a mixture of intermediate (10) (0.00773 mole) and NaHCO_3 (0.0081 mole) in DMF (30 ml). The mixture was stirred at 70°C for 5 hours and brought to room temperature. H_2O and a saturated NaCl solution were added. The mixture was extracted with EtOAc.
- 10 The organic layer was separated, dried (MgSO_4), filtered and the solvent was evaporated. The residue (5g) was purified by column chromatography over silica gel (eluent: $\text{CH}_2\text{Cl}_2/\text{CH}_3\text{OH}$ 98/2; 15-40 μm). The pure fractions were collected and the solvent was evaporated. The residue was taken up in DIPE. The precipitate was filtered off and dried, yielding 1.24 g of compound 1 having
- 15 a melting point of 72°C and represented by the formula



Example B2

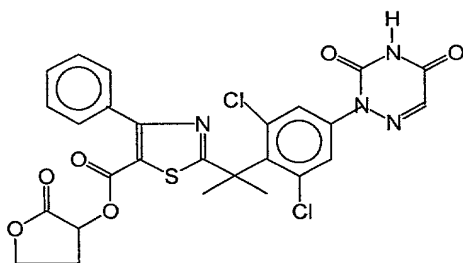
- A solution of 1-bromopentadecane (0.0051 mole) in DMF (18 ml) was added dropwise at room temperature to a mixture of intermediate (10) (0.00483 mole) and NaHCO_3 (0.0051 mole) in DMF (10 ml). The mixture was stirred at 70°C for 5 hours and at 45°C overnight, then brought to room temperature. H_2O and NaCl were added. The mixture was extracted with EtOAc. The organic layer was separated, washed with a saturated NaCl solution, dried (MgSO_4),
- 20

filtered and the solvent was evaporated. The residue (3.8 g) was purified by column chromatography over silica gel (eluent: CH₂Cl₂/CH₃OH 98/2; 15-40 μm). The pure fractions were collected and the solvent was evaporated, yielding 0.49 g of compound 2 having a melting point of 80°C and represented by the formula



Example B3

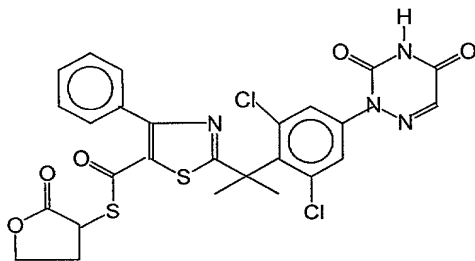
A solution of 3-bromodihydro-2(3H)-furanone (0.0073 mole) in DMF (12 ml) was added dropwise at RT to a mixture of intermediate (13) (0.00695 mole) and NaHCO₃ (0.0073 mole) in DMF (22 ml). The mixture was stirred at 70°C for 2.5 hours, brought to RT and poured out into H₂O. The precipitate was filtered off and taken up in CH₂Cl₂. The organic layer was separated, washed with H₂O, dried (MgSO₄), filtered and the solvent was evaporated. The residue (5.4g) was purified by column chromatography over silica gel (eluent: CH₂Cl₂/CH₃OH 98/2; 15-40 μm). The desired fractions were collected and the solvent was evaporated. The residue was crystallized from CH₃CN, diethyl ether and DIPE. The precipitate was filtered off and dried. Yielding: 1.3g. This fraction was recrystallized from CH₃CN, 2-propanone and diethyl ether. The precipitate was filtered off and dried, yielding 0.89 g of compound 3 having a melting point of 208°C and represented by the formula



Example B4

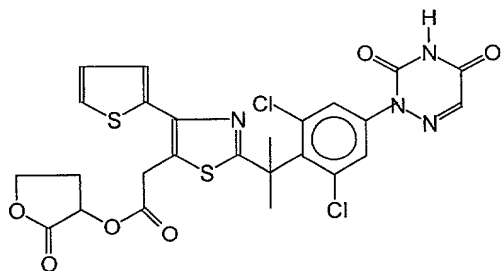
NaHCO₃ (0.00835 mole) was added dropwise at 5°C under a nitrogen flow to a mixture of intermediate (14) (0.00795 mole) in DMF (22 ml). Then a

solution of 3-bromodihydro-2(3H)-furanone (0.00835 mole) in DMF (12 ml) was added dropwise. The mixture was brought to RT and stirred at RT for 30 minutes and then poured out into water and a saturated NaCl solution. A small amount of HCl 3N was added. The precipitate was filtered off and taken up in CH₂Cl₂. The organic layer was separated, dried (MgSO₄), filtered and the solvent was evaporated. The residue (5.1 g) was purified by column chromatography over silica gel (eluent: CH₂Cl₂/CH₃OH 98.5/1.5; 15-40 μm). The pure fractions were collected and the solvent was evaporated. The residue was crystallized from CH₃CN, diethyl ether and DIPE. The precipitate was filtered off and dried. The residue was recrystallized from CH₃CN, diethyl ether and DIPE. The precipitate was filtered off and dried, yielding 0.85 g of compound 4 having a melting point of 212°C and represented by the formula



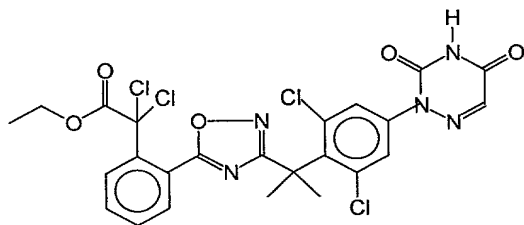
Example B5

A mixture of 3-bromodihydro-2(3H)-furanone (0.00172 mole) in DMF (5 ml) was added dropwise at RT to a mixture of intermediate (16) (0.00172 mole) and NaHCO₃ (0.00172 mole) in DMF (5 ml). The mixture was stirred at 70°C for 5 hours, poured out into water and a saturated NaCl solution and extracted with EtOAc. The organic layer was separated, washed several times with water, dried (MgSO₄), filtered and the solvent was evaporated. The residue (1.2 g) was purified by column chromatography over silica gel (eluent: CH₂Cl₂/CH₃OH 98/2; 15-40 μm). The desired fractions were collected and the solvent was evaporated. The residue was purified again by column chromatography over silica gel (eluent: CH₂Cl₂/2-propanol 97/3; 15-40 μm). The desired fractions were collected and the solvent was evaporated, yielding 0.13 g of compound 5 having a melting point of 110°C and represented by the formula



Example B6

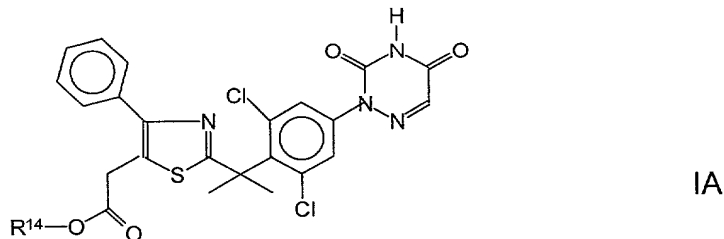
A solution of intermediate (27) (0.001 mole) in ethanol (15 ml) and dichloromethane (15 ml) was stirred and refluxed for one hour. The solvent was evaporated under reduced pressure. The residue was dissolved in CH_2Cl_2 , washed with water, dried (MgSO_4), filtered and the solvent was evaporated. The residue was purified by means of high performance liquid chromatography over Hyperprep C18 (eluent: ((0.5% NH_4OAc in H_2O)/ CH_3CN 90/10)/ CH_3CN (0 min) 80/20, (44 min) 20/80, (57-61 min) 0/100) . The desired fractions were collected and the solvent was evaporated. The residue was stirred in hexane, filtered off, washed and dried under vacuum at 60°C , yielding 0.059 g of compound 6 having a melting point of 157°C and represented by the formula



Example B7

A mixture of intermediate (10) (0.00387 mole) and 1,1'-carbonylbis-1H-imidazole (0.0058 mole) in dichloromethane (40 ml) was stirred at RT for 90 minutes, then cyclohexylmethanol (0.0058 mole) was added. The mixture was stirred at RT overnight, diluted with CH_2Cl_2 and washed twice with an aqueous solution of NaCl . The organic layer was separated, dried (MgSO_4), filtered and the solvent was evaporated. The residue was purified by column chromatography over silica gel (eluent: $\text{CH}_2\text{Cl}_2/\text{EtOAc}$ 50/50). The pure fractions were collected and the solvent was evaporated. The residue was crystallized from EtOAc . The precipitate was filtered off, washed with DIPE and

dried at 50°C overnight, yielding 1.43 g of compound 7 with a molecular weight of 613.5, a melting point of 180°C and represented by the formula



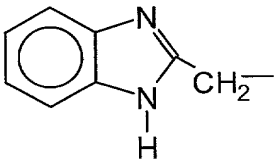
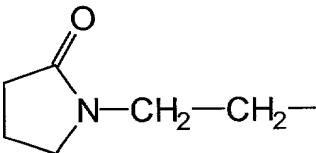
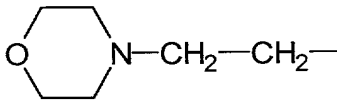
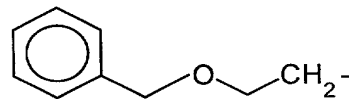
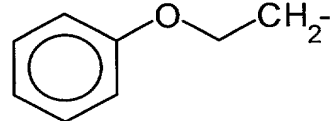
wherein R¹⁴ is cyclohexylmethyl.

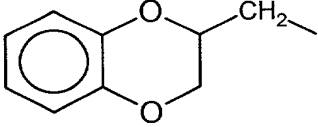
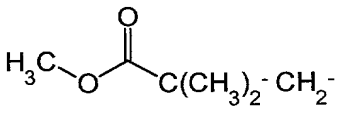
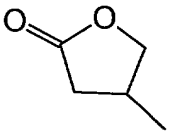
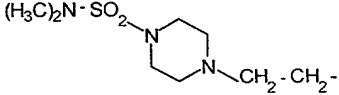
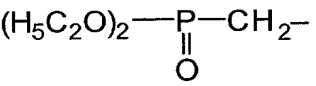
5 Examples B8 to B53

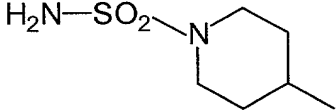
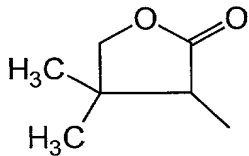
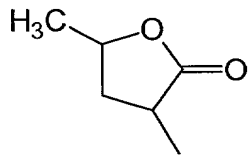
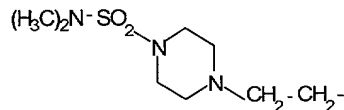
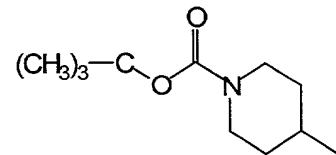
The following table 1 lists compounds of formula (IA) which were prepared according to the procedure of example B7, while replacing cyclohexylmethanol by the relevant alcohol having the formula R¹⁴OH. For the synthesis of compounds 8, 15-18, 21-23, 27, 32-34, 40-42 and 44, the amount of dichloromethane was increased up to 50 ml, and for compound 53 up to 60 ml. For the synthesis of compound 51, dichloromethane was replaced by 45 ml DMF. This table also indicates the melting point (when available) M.P.(expressed in °C) and the yield Y of obtention (expressed as a percentage) of the said compounds.

TABLE 1

COMPOUND NO.	R ¹⁴	M.P. (°C)	Y (%)
8			
9	Isopentyl	148	
10	2-phenyl-ethyl	130	38
11	3-phenyl-n-propyl	114	41
12	2-(N,N'-diisopropylamino)-ethyl	136	

COMPOUND NO.	R ¹⁴	M.P. (°C)	Y (%)
13	2-cyano-ethyl	179	62
14			75
15	3-cyclohexyl-n-propyl	130	
16	4-phenyl-n-butyl	128	
17	Cyclopentylmethyl		
18	3-cyclopropyl-n-propyl		
19			50
20			
21	5-phenyl-n-pentyl	155	
22	Cyclobutylmethyl	150	
23	2-cyclohexylethyl	150	
24			56
25	Cyclopentylmethyl	160	
26	2-isopentenyl	175	
27	1-Cyanoethyl		
28			

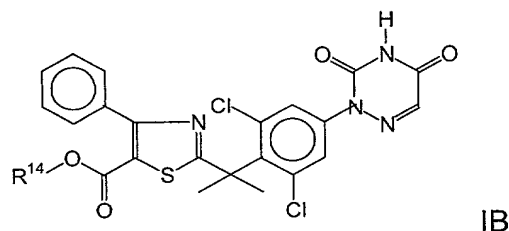
COMPOUND NO.	R ¹⁴	M.P. (°C)	Y (%)
29	4-Cyclohexyl-n-butyl		
30			33
31	2,2,2-trifluoroethyl		67
32	Phenylmethyl		
33	Phenyl		
34	2-methoxyethyl		
35	3-ol-n-propyl		
36	Acetamido	246	29
37	N,N'-diethylacetamido	162	60
38	Dimethylaminoethyl		
39	Styrylmethyl		
40	Cyclohexyl	183	17
41	Toluylacetyloxy	151	71
42		140	37
43	N-methylpiperidinyl		28
44		160	
45			22
46		156	49

COMPOUND NO.	R ¹⁴	M.P. (°C)	Y (%)
47		191	37
48	2,2-diethoxyethyl	156	
49			19
50	Benzylaminoethyl		
51			40
52			22
53			43

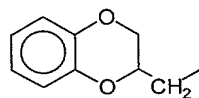
Example B 54

A mixture of 2-bromomethyl-1,4-benzodioxan (0.0044 mole) in DMF (2 ml) was added to a mixture of intermediate (13)(0.0044 mole) and NaHCO₃ (0.0044 mole) in DMF (8 ml). The mixture was stirred at 70°C for 6 hours, then 0.0022 mole of intermediate (13) was added. The mixture was stirred again at 70°C overnight, then poured out into water, acidified with HCl (3N), extracted with EtOAc and washed with water. The organic layer was separated, dried, filtered and the solvent was evaporated. The residue (3.9 g) was purified by column chromatography over silica gel (eluent: CH₂Cl₂/CH₃OH 99/1; 15-40

μm). The pure fractions were collected and the solvent was evaporated. The residue (1.2 g) was crystallized from CH₃CN/DIPE. The precipitate was filtered off and dried, yielding 0.57 g of compound 54 having a molecular weight of 651.5, identified in table 2 below (wherein M.P. and Y have the same meanings as in table 1) and represented by the formula



wherein R¹⁴ is



Example B 55

A mixture of bromo-1-phenyl-2-ethane (0.0065 mole), intermediate (13)(0.0050 mole) and NaHCO₃ (0.0050 mole) in DMF (10 ml) was stirred at 70°C for 12 hours, then poured out on ice, acidified with HCl (3N) until pH 5, extracted with EtOAc and washed several times with water. The organic layer was separated, dried (MgSO₄), filtered and the solvent was evaporated. The residue (3.2 g) was purified by column chromatography over silica gel (eluent: CH₂Cl₂/CH₃OH 99/1; 70-200 μm). The pure fractions were collected and the solvent was evaporated. The residue (0.6 g) was crystallized from diethylether/DIPE. The precipitate was filtered off and dried, yielding 0.42 g of compound 55 of formula (IB), having a molecular weight of 607.5 and identified in table 2 below.

Example B 56

A mixture of phenylbromomethane (0.0065 mole), intermediate (13) (0.0050 mole) and NaHCO₃ (0.0050 mole) in DMF (10 ml) was stirred at 70°C for 12 hours, then cooled and poured out on ice. The precipitate was filtered,

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washed with water and the solvent evaporated. The residue was taken up in HCl (diluted), then water. The organic layer was separated, dried (MgSO_4), filtered and the solvent was evaporated. The residue (3.0 g) was purified by column chromatography over silica gel (eluent: $\text{CH}_2\text{Cl}_2/\text{CH}_3\text{OH}$ 99.5/0.5; 70-200 μm). The pure fractions were collected and the solvent was evaporated. The residue (0.9 g) was crystallized from diethylether/DIPE. The precipitate was filtered off and dried, yielding 0.51 g of compound 56 of formula (IB), having a molecular weight of 593.5 and identified in table 2 below.

Example B 57

10 A mixture of tert-butyl bromoacetate (0.0060 mole), intermediate (13)(0.0050 mole) and NaHCO_3 (0.0050 mole) in DMF (10 ml) was stirred at 70°C for 12 hours, then cooled and poured out into ice water. The precipitate was filtered, washed with H_2O , centrifugated off and taken up in EtOAc. The organic layer was separated, washed with water, dried (MgSO_4), filtered and the solvent was evaporated. The residue (3.0 g) was purified by column chromatography over silica gel (eluent: CH_2Cl_2 ; 70-200 μm). Two fractions were collected and their solvents were evaporated. The first fraction (0.9 g) was crystallized from DIPE. The precipitate was filtered off and dried, yielding 0.53 g of compound 57 of formula (IB), having a molecular weight of 617.5 and identified in table 2 below.

Example B 58

25 A mixture of cyclopropylbromomethane (0.0040 mole) in DMF (10 ml) was added dropwise at RT to a mixture of intermediate (13)(0.0040 mole) and NaHCO_3 (0.0040 mole) in DMF (10 ml). The mixture was stirred at 70°C for 5 hours, poured out on ice, neutralized slowly with HCl (3N) and extracted with EtOAc. The organic layer was separated, washed several times, dried (MgSO_4), filtered and the solvent was evaporated. The residue (2.8 g) was purified by column chromatography over silica gel (eluent: $\text{CH}_2\text{Cl}_2/\text{EtOAc}$ 92/8; 15-40 μm ; $\text{CH}_3\text{CN}/\text{NH}_4\text{Ac}$ 1% 60/40 10 μm). The pure fractions were collected and the solvent was evaporated, yielding 0.34 g of compound 58 of formula (IB), having a molecular weight of 557.5 and identified in table 2 below.

Example B 59

A mixture of chloro-1 dimethylamino-2 ethane (0.0044 mole) and NaHCO₃ (0.0087 mole) in DMF (10 ml) was stirred at RT for 30 minutes. Intermediate (13)(0.0050 mole) was added portionwise. The mixture was stirred at 70°C overnight, cooled, poured out onto water and neutralized with HCl 3N. The precipitate was filtered, washed with water and taken up in CH₂Cl₂. The organic layer was separated, dried (MgSO₄), filtered and the solvent was evaporated. The residue (2.4 g) was purified by column chromatography over silica gel (eluent: CH₂Cl₂/CH₃OH 94/6; 15-40 µm). The pure fractions were collected and the solvent was evaporated, yielding 0.58 g of compound 59 of formula (IB), having a molecular weight of 574.5 and identified in table 2 below.

Example B 60

A mixture of 1-chloroethyl ethylcarbonate (0.0065 mole), intermediate (13)(0.0050 mole), NaHCO₃ (0.0050 mole) and potassium iodide (0.0050 mole) in DMF (10 ml) was stirred at 70°C for 12 hours, then cooled and poured out into ice water. The precipitate was filtered off, washed with a diluted solution of HCl, washed with water, centrifugated and taken up in EtOAc. The organic layer was separated, dried (MgSO₄), filtered and the solvent was evaporated. The residue (3.3 g) was purified by column chromatography over silica gel (eluent: CH₂Cl₂; 70-200 µm). The desired fractions were collected and the solvent was evaporated. The residue (0.7 g) was crystallized from diethylether/DIPE. The precipitate was filtered off and dried, yielding 0.34 g of compound 60 of formula (IB), having a molecular weight of 619.5 and identified in table 2 below.

Example B 61

A mixture of ethyl bromoacetate (0.0040 mole) in DMF (2 ml) was stirred at RT. A solution of intermediate (13)(0.0040 mole) and NaHCO₃ (0.0040 mole) in DMF (8 ml) was added. The mixture was stirred at 70°C for 2 hours, cooled, poured out into ice water and acidified with HCl 3N. The precipitate was filtered off, washed with water and taken up in EtOAc. The organic layer was separated, washed with water, dried (MgSO₄), filtered and the solvent was

evaporated. The residue (2.2 g) was purified by column chromatography over silica gel (eluent: CH₂Cl₂/CH₃OH 99/1; 15-40 μm). The pure fractions were collected and the solvent was evaporated. The residue (1.2 g) was crystallized from diethylether. The precipitate was filtered off and dried, yielding 0.98 g
5 compound 61 of formula (IB), having a molecular weight of 589.5 and identified in table 2 below.

Example B 62

A mixture of bromo-1-phenyl-3-propane (0.0065 mole), intermediate (13)(0.0050 mole), NaHCO₃ (0.0050 mole) in DMF (10 ml) was stirred at 70°C
10 for 12 hours, then poured out into ice water and extracted with EtOAc. The organic layer was separated, washed with a diluted solution of HCl, washed with water, dried (MgSO₄), filtered and the solvent was evaporated. The residue (3.5 g) was purified by column chromatography over silica gel (eluent: CH₂Cl₂; 70-200 μm). The pure fractions were collected and the solvent was
15 evaporated. The residue (1.2 g) was crystallized from diethylether/DIPE. The precipitate was filtered off and dried, yielding 0.85 g of compound 62 of formula (IB), having a molecular weight of 621.5 and identified in table 2 below.

Example B 63

A mixture of 2-(chloromethyl)benzimidazole (0.0044 mole) in DMF (5 ml)
20 was added dropwise at RT to a mixture of intermediate (13)(0.0044 mole) and NaHCO₃ (0.0044 mole) in DMF (5 ml). The mixture was stirred at 70°C for 15 hours, cooled and poured out on ice. The precipitate was filtered off, washed with water several times, centrifugated off and taken up in EtOAc. The organic layer was separated, washed with water, dried (MgSO₄), filtered and the
25 solvent was evaporated. The residue (3.5 g) was purified by column chromatography over silica gel (eluent: CH₂Cl₂/CH₃OH 98/2; 15-40 μm). The pure fractions were collected and the solvent was evaporated. The residue (0.9 g) was crystallized from diethylether. The precipitate was filtered off and dried, yielding 0.4 g of compound 63 of formula (IB), having a molecular weight of
30 633.5 and identified in table 2 below.

Example B 64

A mixture of cyclobutyl bromomethane (0.0040 mole) in DMF (2 ml) was

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added at RT to a mixture of intermediate (13)(0.0040 mole) and NaHCO_3 (0.0040 mole) in DMF (8 ml). The mixture was stirred at 70°C overnight, then cooled, poured out into ice water and extracted with EtOAc. The organic layer was separated, washed with water, dried (MgSO_4), filtered and the solvent was evaporated. The residue (2.1 g) was purified by column chromatography over silica gel (eluent: $\text{CH}_2\text{Cl}_2/\text{CH}_3\text{OH}$ 99.25/0.75; 15-40 μm , $\text{CH}_3\text{CN}/\text{NH}_4\text{Ac}$ 75/25; 10 μm). The pure fractions were collected and the solvent was evaporated. The residue (0.9 g) was crystallized from diethylether. The precipitate was filtered off and dried, yielding 0.44 g of compound 64 of formula (IB), having a molecular weight of 571.5 and identified in table 2 below.

Example B 65

A mixture of bromo-3-propanol-1 (0.0050 mole), intermediate (13)(0.0046 mole), NaHCO_3 (0.0046 mole) in DMF (10 ml) was stirred at 70°C for 6 hours, then cooled and poured out into ice water. The precipitate was filtered, washed with a diluted solution of HCl and dried. The residue was taken up in CH_2Cl_2 . The organic layer was separated, washed with water, dried (MgSO_4), filtered and the solvent was evaporated. The residue (2.6 g) was purified by column chromatography over silica gel (eluent: $\text{CH}_2\text{Cl}_2/\text{CH}_3\text{OH}$ 97.5/2.5; 15-40 μm). The desired fractions were collected and the solvent was evaporated. The residue (0.8 g) was crystallized from DIPE. The precipitate was filtered off and dried, yielding 0.55 g of compound 65 of formula (IB), having a molecular weight of 561.5 and identified in table 2 below.

Example B 66

A mixture of bromo-1 methyl-3 butene-2 (0.0040 mole) in DMF (2 ml) was added at RT to a solution of intermediate (13) (0.0040 mole) and NaHCO_3 (0.0040 mole) in DMF (8 ml). The mixture was stirred at 70°C for 20 hours, cooled, poured out into ice water, acidified with HCl 3N and then extracted with EtOAc. The organic layer was separated, dried (MgSO_4), filtered and the solvent was evaporated. The residue (2.0 g) was purified by column chromatography over silica gel (eluent: $\text{CH}_2\text{Cl}_2/\text{CH}_3\text{OH}$ 99.5/0.5; 70-200 μm). The desired fractions were collected and the solvent was evaporated. The residue (0.5 g) was purified again by column chromatography over silica gel

(eluent: CH₃CN/0.5%NH₄Oac 70/30; 10 µm). The pure fractions were collected and the solvent was evaporated, yielding 0.25 g of compound 66 of formula (IB), having a molecular weight of 571.5 and identified in table 2 below.

Example B 67

5 A mixture of iodomethyl trimethylacetate (0.0119 mole), intermediate (13)(0.0040 mole) and NaHCO₃ (0.0050 mole) in DMF (20 ml) was stirred at 70°C for 12 hours, then poured out on ice and acidified with HCl 3N. The precipitate was filtered off and dried. The residue was taken up in CH₂Cl₂. The organic layer was separated, dried (MgSO₄), filtered and the solvent was
10 evaporated. The residue (2.3 g) was purified by column chromatography over silica gel (eluent: CH₂Cl₂/CH₃OH 98.5/1.5; 15-40 µm to CH₃COONH₂/CH₃CN 25/75; 10 µm). The pure fractions were collected and the solvent was evaporated, yielding 0.25 g of compound 67 of formula (IB), having a molecular weight of 617.5 and identified in table 2 below.

15 Example B 68

A mixture of N,N-diethyl bromoacetamide (0.0065 mole), intermediate (13) (0.0050 mole) and NaHCO₃ (0.0050 mole) in DMF (10 ml) was stirred at 70°C for 12 hours, cooled and poured out on ice. The precipitate was filtered, washed with water, centrifugated off and taken up in EtOAc. The organic layer
20 was separated, washed with a diluted solution of HCl, washed with water, dried (MgSO₄), filtered and the solvent was evaporated. The residue (3.1 g) was purified by column chromatography over silica gel (eluent: CH₂Cl₂/CH₃OH 98.5/1.5; 15-40 µm). The pure fractions were collected and the solvent was evaporated. The residue (1.4 g) was crystallized from CH₃CN and diethylether.
25 The precipitate was filtered off and dried, yielding 0.7 g of compound 68 of formula (IB), having a molecular weight of 616.5 and identified in table 2 below.

Example B 69

A mixture of 4-chloro-1,3-dioxolan-2-one (0.0031 mole), intermediate (13) (0.0024 mole), NaHCO₃ (0.0024 mole) and potassium iodide (0.0024
30 mole) in DMF (6 ml) was stirred at 70°C for 5 hours, poured out into ice water and acidified with HCl 3N. The precipitate was filtered off, washed with water and taken up in CH₂Cl₂. The organic layer was separated, dried (MgSO₄),

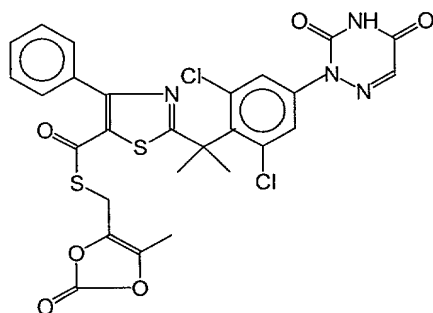
filtered and the solvent was evaporated. The residue (1.8 g) was purified by column chromatography over silica gel (eluent: CH₂Cl₂/CH₃OH 98/2; 15-40 μm). The pure fractions were collected and the solvent was evaporated, yielding 0.65 g of compound 69 of formula (IB), having a molecular weight of 589.5 and identified in table 2 below.

Example B 70

A mixture of 4-bromomethyl-5-methyl-1,3-dioxol-2-one (0.0034 mole), intermediate (13)(0.0026 mole), NaHCO₃ (0.0026 mole) in DMF (6 ml) was stirred at 70°C for 12 hours, then poured out into ice water and acidified with HCl 3N. The precipitate was filtered, washed with water and taken up in CH₂Cl₂. The organic layer was separated, dried (MgSO₄), filtered and the solvent was evaporated. The residue (1.8 g) was purified by column chromatography over silica gel (eluent: CH₂Cl₂/CH₃OH 98/2; 15-40 μm) then over Kromasil (eluent: CH₃CN/CH₃OH 80/20; 3.5 μm). The pure fractions were collected and the solvent was evaporated, yielding 0.28 g of compound 70 of formula (IB), having a molecular weight of 615.5 and identified in table 2 below.

Example B 71

A mixture of 4-bromomethyl-5-methyl-1,3-dioxol-2-one (0.0046 mole), intermediate (14)(0.0035 mole), NaHCO₃ (0.0035 mole) in DMF (10 ml) was stirred at 70°C for 5 hours, poured out into ice water and acidified with HCl 3N. The precipitate was filtered, washed with water and taken up in CH₂Cl₂. The organic layer was separated, dried (MgSO₄), filtered and the solvent was evaporated. The residue (2.5 g) was purified by column chromatography over silica gel (eluent: CH₂Cl₂/CH₃OH 99/1; 15-40 μm) then over Kromasil (eluent: CH₃CN/AcNH₄ 65/35; 10 μm). The pure fractions were collected and the solvent was evaporated, yielding 0.36 g (33%) of compound 71, having a molecular weight of 631.5 and a melting point of 97°C and represented by the formula:



Example B 72

4-bromomethyl-5-methyl-1,3-dioxol-2-one (0.0081 mole) was dissolved in DMF (20 ml). This solution was added dropwise to intermediate (10)(0.0077 mole) and NaHCO_3 (0.0081 mole) in DMF (30 ml) under nitrogen atmosphere. The reaction mixture was stirred at 50°C for 3 hours, poured out into water (+ NaCl) and extracted three times with EtOAc. The organic layer was separated, dried (MgSO_4), filtered and the solvent was evaporated. The residue was purified by high performance liquid chromatography over silica gel (eluent: $\text{CH}_2\text{Cl}_2/\text{CH}_3\text{CN}$). The desired fractions were collected and the solvent was evaporated, yielding 0.86 g of an oily fraction which was stirred in hexane/EtOAc (1:1) until a white precipitate was formed. This precipitate was filtered off, washed with DIPE and dried overnight, yielding 0.58 g of compound 72, having a molecular weight of 629.5 and a melting point of 149°C and represented by the formula:

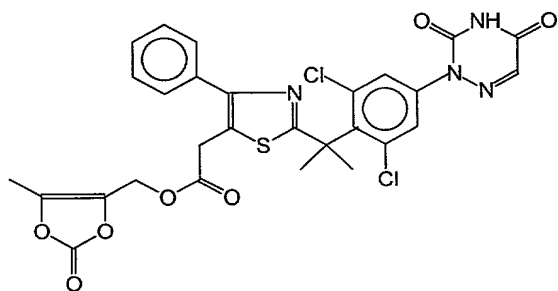
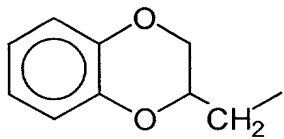
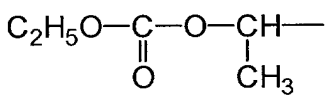
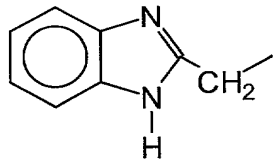
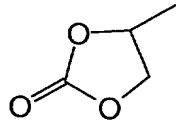
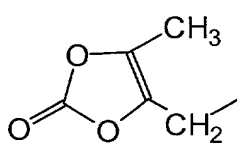


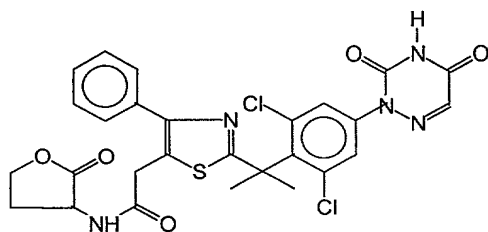
TABLE 2

COMPOUND NO.	R ¹⁴	M.P. (°C)	Y (%)
54		182	53
55	Phenyl-2 ethyl	146	20
56	Phenylmethyl	167	30
57	Tert-butyl acetyl	165	17
58	Cyclopropylmethyl	100	13
59	Dimethylaminoethyl	204	22
60		163	11
61	Ethylacetyl	198	
62	Phenyl-3 propyl	165	27
63		172	14
64	Cyclobutylmethyl	80	33
65	Hydroxy-3 propyl	85	31
66	Methyl-3-butene-2-yl	90	11
67	Trimethylacetyl	80	10
68	Diethylacetamido	157	
69		90	36

COMPOUND NO.	R ¹⁴	M.P. (°C)	Y (%)
70		102	14

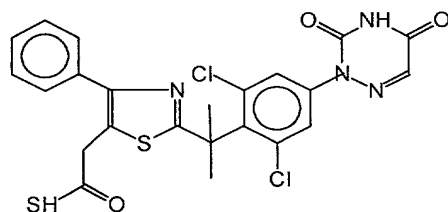
Example B 73

A mixture of intermediate (10) (0.00387 mole) and 1,1'-carbonylbis-1H-imidazole (0.0058 mole) in dichloromethane (40 ml) was stirred at RT for 90 minutes, then 3-aminodihydro-2(3H)furanone (0.0058 mole) was added. The mixture was stirred at RT overnight, diluted with CH₂Cl₂ and washed twice with an aqueous solution of NaCl. The organic layer was separated, dried (MgSO₄), filtered and the solvent was evaporated. The residue was filtered over silica gel (eluent: CH₂Cl₂/EtOAc 50/50). The product fractions were collected and the solvent was evaporated. The residue was crystallized from EtOAc. The residue was stirred in DIPE, filtered off, washed and dried at 50°C under vacuum for two days, yielding 1.43 g (62%) of compound 73 having a molecular weight of 600.5 and represented by the formula

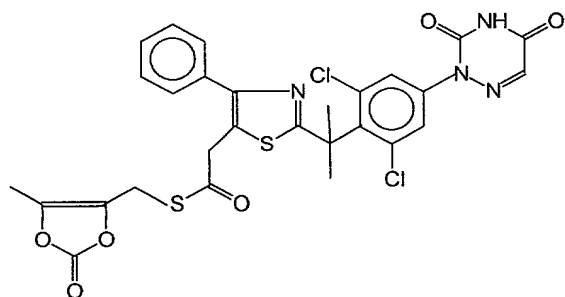


Examples B 74 and B 75

A mixture of intermediate (10) (0.0156 mole) and 1,1'-carbonylbis-1H-imidazole (0.0232 mole) in DMF(160 ml) was stirred at RT for 3 hours, and then treated with an excess of hydrogen sulfide for 20 minutes at RT, then with nitrogen overnight. Half of this reaction mixture, containing 0.0078 mole of compound 74 represented by the formula



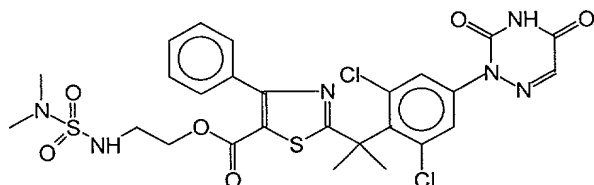
in 80 ml DMF, was treated with a solution of 4-bromomethyl-5-methyl-1,3-dioxol-2-one (0.013 mole) in DMF (20 ml). The reaction mixture was stirred for one hour, then poured out into water and extracted twice with EtOAc. The organic layer was separated, dried (MgSO₄), filtered and the solvent was evaporated. The residue was purified over silica gel on a glass filter (eluent: CH₂Cl₂/EtOAc 92.5/7.5). The pure fractions were collected and the solvent was evaporated. The residue was stirred in DIPE, filtered off, washed and dried under vacuum for one hour, yielding 2.68 g (54%) of compound 75 represented by the formula



Example B 76

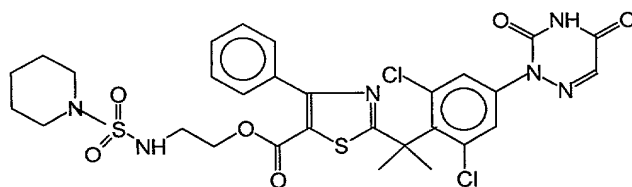
1,1'-carbonylbis-1H-imidazole (0.0017 mole) was added to a mixture of intermediate (13) (0.0014 mole) in DMF (6 ml). The mixture was stirred at 40°C for one hour. A solution of N,N-dimethylethanolaminesulfonamide (0.0028 mole) and 1,8-diazabicyclo (5.4.0) undecene-7 (0.0014 mole) in DMF (3 ml) was added. The mixture was stirred at 40°C for 3 hours, then brought to RT, poured out into water, acidified with HCl 3N, filtered and washed with water. The precipitate was filtered off and dried. The residue was taken up in diethyl ether. The organic layer was separated, dried (MgSO₄), filtered and the solvent was evaporated. The residue was crystallized from diethyl ether/CH₃CN/DIPE, yielding 0.77 g (65%) of compound 76 having a molecular weight of 653.5 g, a

melting point of 150°C and being represented by the formula



Example B 77

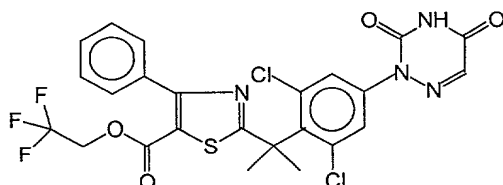
1,1'-carbonylbis-1H-imidazole (0.0013 mole) was added at RT to a mixture of intermediate (13) (0.0010 mole) in DMF (4 ml). The mixture was stirred at 40°C for 45 minutes. A mixture of N-(2-hydroxyethyl)-1-piperidinesulfonamide (0.0019 mole) and 1,8-diazabicyclo (5.4.0) undecene-7 (0.0010 mole) in DMF (2 ml) was added fastly. The mixture was stirred at 40°C for 90 minutes, then brought to RT, poured out into water and acidified with HCl 3N. The precipitate was filtered off and dried. The residue was taken up in CH₂Cl₂, then filtered and dried again and then purified by column chromatography over silica gel (eluent: CH₂Cl₂/CH₃OH 98.5/1.5; 15-40 μm). The pure fractions were collected and the solvent was evaporated. The residue (0.34 g) was taken up in DIPE. The precipitate was filtered off and dried, yielding 0.18 g (57%) of compound 77 having a molecular weight of 693.5 g, a melting point of 126°C and being represented by the formula



Example B 78

1,1'-carbonylbis-1H-imidazole (0.0030 mole) was added at RT to a mixture of intermediate (13) (0.0024 mole) in DMF (12 ml). The mixture was stirred at 40°C for one hour. A solution of 2,2,2-trifluoroethanol (0.0048 mole) and 1,8-diazabicyclo (5.4.0) undecene-7 (0.0024 mole) in DMF (5 ml) was added. The mixture was stirred at 40°C for 2 hours, poured out on ice/HCl 3N, filtered and washed with water. The precipitate was taken up in CH₂Cl₂. The

organic layer was separated, dried (MgSO₄), filtered and the solvent was evaporated. The residue was crystallized from diethyl ether, then filtered off and dried, yielding 0.51 g (31%) of compound 78 having a molecular weight of 583.5 g, a melting point of 180°C and being represented by the formula

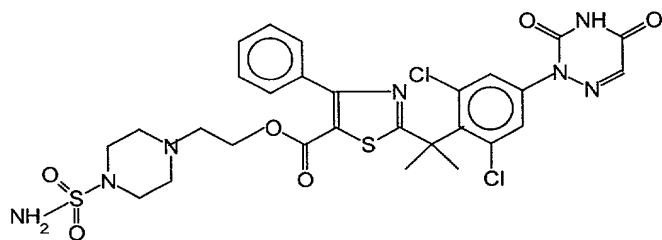


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Example B 79

1,1'-carbonylbis-1H-imidazole (0.0050 mole) was added to a mixture of intermediate (13) (0.0040 mole) in DMF (15 ml). The mixture was stirred at 40°C for one hour. A solution of N-(2-hydroxyethyl)-N'-piperazinesulfonamide (0.0104 mole) and 1,8-diazabicyclo (5.4.0) undecene-7 (0.0040 mole) in DMF (10 ml) was added. The mixture was stirred at 40°C for 2 hours, then brought to RT, poured out on ice water and acidified with HCl 3N. The precipitate was filtered, washed with water and taken up in CH₂Cl₂/CH₃OH. The organic layer was separated, dried (MgSO₄), filtered and the solvent was evaporated. The residue (2.7 g) was purified by column chromatography over silica gel (eluent: CH₂Cl₂/CH₃OH 96/4; 15-40 μm). The pure fractions were collected and the solvent was evaporated, yielding 0.3 g (10%) of compound 79 having a molecular weight of 694.5 g, a melting point of 133°C and being represented by the formula

15



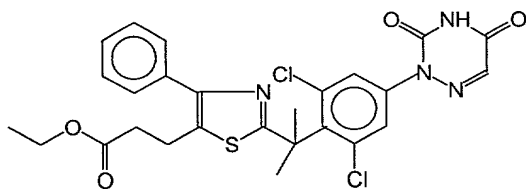
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Example B80

A mixture of intermediate (8) (0.0097 mole) and -bromo- -oxo- benzenepentanoic acid ethyl ester (0.0126 mole) in ethanol (150 ml) was stirred and refluxed overnight. The solvent was evaporated and the residue

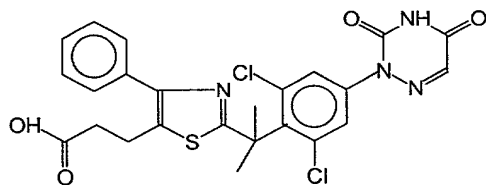
was taken up in methylene chloride. The organic layer was separated, washed with a 10% solution of K_2CO_3 then with water, dried ($MgSO_4$), filtered and the solvent was evaporated. The residue (5.7 g) was purified by column chromatography over silica gel (eluent: CH_2Cl_2/CH_3OH 98.5/1.5; 15-40 μm).

- 5 The pure fractions were collected and the solvent was evaporated, yielding 3.2 g (59%) of compound 80 having a molecular weight of 559.5 g, a melting point of 155°C and being represented by the formula



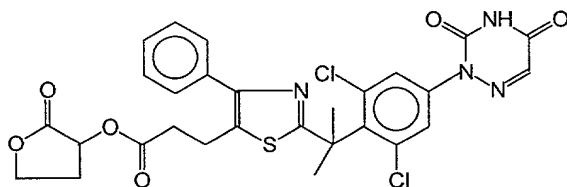
Example 81

- 10 A mixture of compound 80 (0.0032 mole) and sodium hydroxide (0.0096 mole) in methanol (20 ml) and THF (20 ml) was stirred at RT for 12 hours, poured out on ice, acidified with HCl 1N and extracted with EtOAc. The organic layer was separated, dried ($MgSO_4$), filtered and the solvent was evaporated, yielding 1.7 g of a compound of the formula



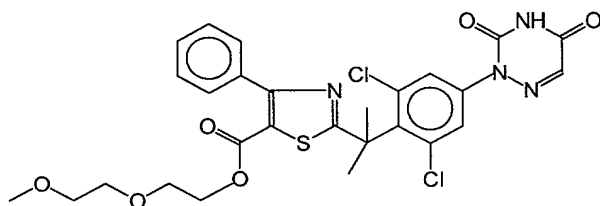
- 15 which, after crystallization from diethyl ether, shows a melting point of 186°C. A mixture of γ -bromo- γ -butyrolactone (0.0021 mole) in DMF (5 ml) was added dropwise at RT to a mixture of the compound obtained in the preceding step (0.0021 mole) and $NaHCO_3$ (0.0021 mole) in DMF (5 ml). The mixture was stirred at 70°C for five hours, poured out on ice, neutralized slowly with HCl (3N) and extracted with EtOAc and washed with water. The organic layer was separated, washed several times with water, dried ($MgSO_4$), filtered and the solvent was evaporated. The residue (1.1 g) was purified by column chromatography over silica gel (eluent: CH_2Cl_2/CH_3OH 99/1; 15-40 μm). The pure fractions were collected and the solvent was evaporated. The residue (1.2
- 20
- 25

g) was crystallized from diethylether and CH₃CN. The precipitate was filtered off and dried, yielding 0.25 g (19%) of compound 81 having a molecular weight of 615.5 g, a melting point of 190°C and being represented by the formula



5 Example B 82

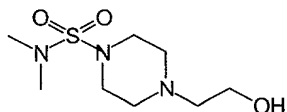
Intermediate (13) (0.0050 mole) was added to DMF (20 ml) under a nitrogen flow. 1,1'-carbonylbis-1H-imidazole (0.0062 mole) was added and the mixture was stirred at 40°C for one hour. Then 2-(2-methoxyethoxy) ethanol (0.0099 mole) and 1,8-diazabicyclo (5.4.0) undecene-7 (0.005 mole) were added and the resulting mixture was stirred at 40°C for 12 hours, cooled and then diluted with diethyl ether. The organic layer was separated, washed with HCl 3N then with water, dried (MgSO₄), filtered and the solvent was evaporated. The residue (2.5 g) was purified by column chromatography over silica gel (eluent: CH₂Cl₂/CH₃OH 98.5/1.5; 15-40 µm). The pure fractions were collected and the solvent was evaporated. The residue (1.5 g) was crystallized from DIPE. The precipitate was filtered off and dried, yielding 1.03 g (34%) of compound 82 having a molecular weight of 605.5 g, a melting point of 151°C and being represented by the formula



20 Example B 83

A mixture of N,N-dimethyl-1-piperazinesulfonamide (0.0423 mole) in methanol (100 ml) and methylene chloride (30 ml) was treated with an excess of gaseous ethylene oxide at 5°C for 90 minutes. The reaction mixture was stirred at RT for 3 hours. The solvent was evaporated, then co-evaporated with toluene. The residue was stirred overnight in 7N NH₃/CH₃OH and the solvent

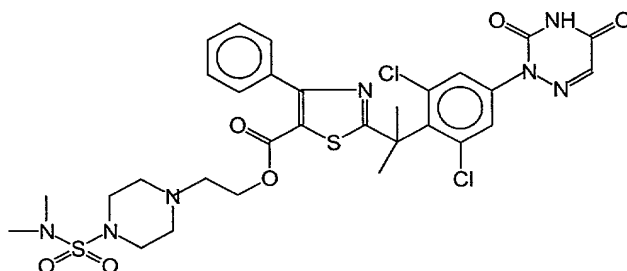
was evaporated, then co-evaporated with toluene. The residue (10.3 g) was purified over silica gel on a glass filter (eluent: CH₂Cl₂/CH₃OH 92.5/7.5). The desired fractions were collected and the solvent was evaporated, then co-evaporated with toluene, yielding 6.9 g (69 %) of a compound 83 represented by the formula



which after crystallization from diethyl ether, shows a melting point of 186°C.

Example B 84

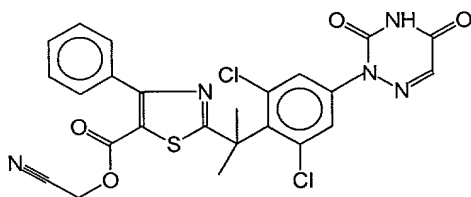
Intermediate (13) (0.0036 mole) was added to DMF (15 ml) under a nitrogen flow. 1,1'-carbonylbis-1H-imidazole (0.0045 mole) was added and the mixture was stirred at 40°C for one hour. Then a solution of compound 83 (0.0072 mole) and 1,8-diazabicyclo (5.4.0) undecene-7 (0.0036 mol) was added over two minutes and the resulting mixture was stirred at 40°C for 5 hours, brought to RT, poured out into water, filtered and taken up in CH₂Cl₂. The organic layer was separated, washed with water, dried (MgSO₄), filtered and the solvent was evaporated. The residue (2.5 g) was purified by column chromatography over silica gel (eluent: CH₂Cl₂/CH₃OH 97/3; 15-40 μm). The pure fractions were collected and the solvent was evaporated. The residue (1.3 g) was crystallized from CH₃CN and diethyl ether. The precipitate was filtered off and dried, yielding 1.0 g of compound 84 having a molecular weight of 722.7 g, a melting point of 220°C and being represented by the formula



Example B 85

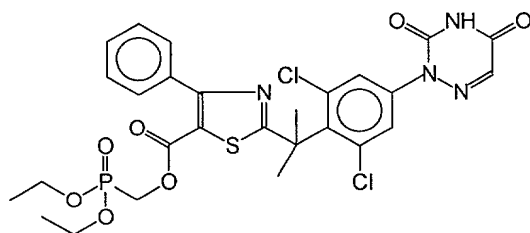
A mixture of bromoacetonitrile (0.0040 mole) in DMF (2 ml) was added at RT to a solution of intermediate (13) (0.0040 mole) and NaHCO₃ (0.0040

mole) in DMF (8 ml). The mixture was stirred at 70°C overnight, cooled, poured out into ice water, acidified with HCl (3N) and then extracted with EtOAc. The organic layer was separated, washed with water, dried (MgSO₄), filtered and the solvent was evaporated. The residue (1.9 g) was purified by column chromatography over silica gel (eluent: CH₂Cl₂/CH₃OH 99.25/0.75; 15-40 μm). The fractions were collected and, after evaporation of their solvent, purified again by column chromatography over silica gel (eluent: CH₂Cl₂/CH₃OH 99.25/0.75; 15-40 μm). The pure fractions were collected and the solvent evaporated, yielding 0.26 g (12%) of compound 85 having a molecular weight of 542.5 g and being represented by the formula



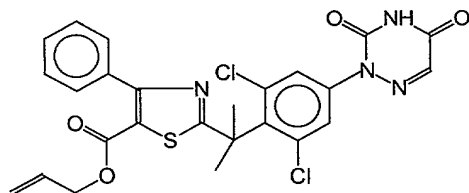
Example B 86

Intermediate (13) (0.0034 mole) was added under a nitrogen flow to DMF (25 ml). 1,1'-carbonylbis-1H-imidazole (0.0043 mole) was added and the mixture was stirred at 40°C for one hour. (Hydroxymethyl) phosphonate diethyl ester (0.0068 mole) and 1,8-diazabicyclo (5.4.0) undecene-7 (0.0034 mole) were added and the mixture was stirred at 40°C for 5 hours, then brought to room temperature, poured out into water and acidified with HCL 3N. The precipitate was filtered off and taken up in methylene chloride. The organic layer was separated, washed with water, dried (MgSO₄), filtered and the solvent was evaporated. The residue (3.0 g) was purified by column chromatography over silica gel (eluent: CH₂Cl₂/CH₃OH 98/2; 15-40 μm). The fractions were collected and the solvent was evaporated. The residue (1.4 g) was taken up in DIPE. The precipitate was filtered off and dried, yielding 1.3 g of compound 86 having a molecular weight of 653.5 g, a melting point of 88°C and being represented by the formula



Example B 87

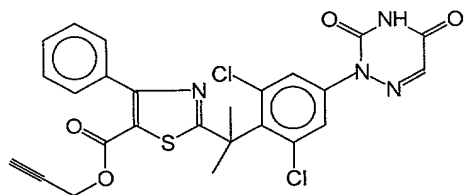
A mixture of bromo-3 propylene-1 (0.0040 mole) in DMF (2 ml) was added at RT to a solution of intermediate (13) (0.0040 mole) and NaHCO₃ (0.0040 mole) in DMF (8 ml). The mixture was stirred at 70°C overnight, poured out into ice water and extracted with EtOAc. The organic layer was separated, washed with water, dried (MgSO₄), filtered and the solvent was evaporated. The residue (2.2 g) was purified by column chromatography over silica gel (eluent: CH₂Cl₂/CH₃OH 99.5/0.5; 35-70 μm). The fractions were collected and the solvent evaporated. The residue (0.8 g) was crystallized from acetonitrile. The precipitate was filtered off and dried, yielding 0.31 g (15%) of compound 87 having a molecular weight of 543.5 g, a melting point of 172°C and being represented by the formula



Example B 88

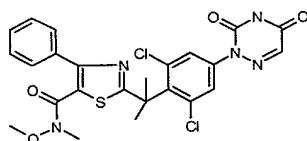
A mixture of bromoacetylene (0.0040 mole) in DMF (2 ml) was added at RT to a solution of intermediate (13) (0.0040 mol) and NaHCO₃ (0.0040 mole) in DMF (8 ml). The mixture was stirred at 70°C overnight, poured out into ice water and extracted with EtOAc. The organic layer was separated, washed with water, dried (MgSO₄), filtered and the solvent was evaporated. The residue (2.5 g) was purified by column chromatography over silica gel (eluent: CH₂Cl₂; column: 70-200 μm). The desired fractions were collected and the solvent evaporated. The residue was purified again by column chromatography

over silica gel (eluent: CH₃CN/NH₄Oac 68/32; column Kromasil C18 10 μm). The pure fractions were collected and the solvent was evaporated. The residue (0.6 g) was crystallized from diethyl ether. The precipitate was filtered off and dried, yielding 0.41 g of compound 88 having a molecular weight of 541.5 g, a melting point of 180°C and being represented by the formula



EXAMPLE B89

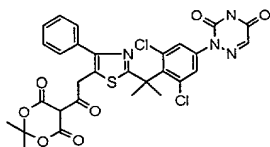
1,1'-carbonylbis-1H-imidazole (0.0048 mole) was added to a mixture of intermediate (13) (0.00397 mole) in methylene chloride (36 ml). The resulting mixture was stirred at room temperature for 24 hours, then HCl 1N was added. The organic layer was separated, dried (MgSO₄), filtered and the solvent was evaporated. The residue (1.95 g) was purified by flash column chromatography over silica gel (eluent: CH₂Cl₂/CH₃OH 99/1; 35-70 μm). The pure fractions were collected and the solvent was evaporated, yielding 1.16 g (53%) of a compound 89 having a molecular weight of 546.4 g, a melting point of 112°C and being represented by the formula



EXAMPLE B 90

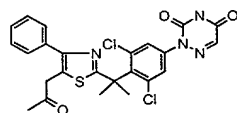
A mixture of intermediate (10) (0.02 mole) and 1,1'-carbonylbis-1H-imidazole (0.03 mole) in methylene chloride (250 ml) was stirred for 2 hours at room temperature. 2,2-dimethyl-1,3-Dioxane-4,6-dione (0.03 mole) was added and the resulting reaction mixture was stirred overnight at room temperature. A solid was formed. Water and a saturated aqueous NaCl solution were added. The product was extracted with CH₂Cl₂/THF (70/30). The organic layer was

separated, dried, filtered and the solvent evaporated, yielding 12.9 g of a product, part of which (2.2 g) was purified over silica gel on a glass filter (eluent: CH₂Cl₂/CH₃OH 95/5). The fractions were collected and the solvent was evaporated. The residue was stirred in DIPE, filtered off and dried, yielding 0.7 g of a compound 90 having a molecular weight of 679.5 g and being represented by the formula



10 EXAMPLE B91

A mixture of compound 90 (0.013 mole) in acetic acid (50 ml) and water (100 ml) was stirred and refluxed (oil bath) for 2 hours with evolution of CO₂. The mixture was poured out into iced water, then extracted with CH₂Cl₂. The separated organic layer was dried, filtered and the solvent evaporated. The residue was purified over silica gel on a glass filter (eluent: CH₂Cl₂/CH₃OH 97/3). The fractions were collected and the solvent was evaporated. The residue was crystallized from CH₃CN (10 ml), filtered off, washed with DIPE and dried, yielding 3.4 g of a compound 91 having a molecular weight of 515.4 g and being represented by the formula

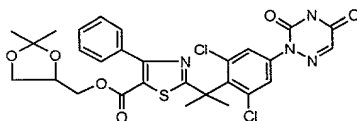


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EXAMPLE B92

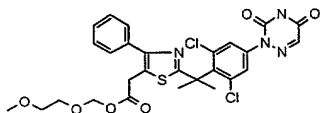
25 A mixture of intermediate (13) (0.002 mole) in DMF (10 ml) was stirred. 1,1'-carbonylbis-1*H*-imidazole (0.0025 mole) was added. The mixture was stirred at 40°C for one hour. 2,2-dimethyl-1,3-Dioxolane-4-methanol (0.004 mole) then 2,3,4,6,7,8,9,10-octahydro- Pyrimido[1,2-*a*]azepine (0.002 mole) were added.

The mixture was stirred at 40°C for two hours, poured out on ice, acidified with HCl 3N and extracted with CH₂Cl₂. The organic layer was separated, washed several times with water, dried (MgSO₄), filtered and the solvent was evaporated. The residue (1.2 g) was purified by column chromatography over silica gel (eluent: CH₂Cl₂/CH₃OH 97/3; 15-40µm). The pure fractions were collected and the solvent was evaporated. The residue (1 g) was crystallized from diethyl ether/DIPE, then the precipitate was filtered off and dried, yielding 0.66g (54%) of a compound 92 having a molecular weight of 617.5 g, a melting point of 163°C and being represented by the formula



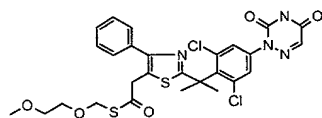
EXAMPLE B93

1-(chloromethoxy)-2-methoxy-Ethane (0.0116 mole) was added dropwise to a solution of intermediate (10) (0.0078 mole) and 1*H*-imidazole (0.0116 mole) in DMF (80 ml), stirred at room temperature. The reaction mixture was stirred for 16 hours at room temperature, then poured out into water and the aqueous layer was extracted with EtOAc. The separated organic layer was dried, filtered and the solvent evaporated, yielding 2.4 g of a fraction which was purified by column chromatography over silica gel (Merck Art. 11695; eluent: CH₂Cl₂/CH₃CN from 85/15 to 80/20). The desired fractions were collected and the solvent was evaporated, then the product was crystallized from EtOAc/hexane 1/1 (20 ml), filtered off and dried, yielding 0.11 g of a compound 93 having a molecular weight of 605.5 g and being represented by the formula



EXAMPLE B94

1-(chloromethoxy)-2-methoxy-Ethane (0.0116 mole) in DMF (10 ml) was added dropwise to compound B74 (0.00783 mole). The reaction mixture was stirred
5 for 16 hours at room temperature, then poured out into water and this mixture was extracted with EtOAc. The separated organic layer was dried, filtered and the solvent evaporated under reduced pressure, yielding 4.7 g of a fraction which was purified by column chromatography over silica gel (eluent: CH₂Cl₂/EtOAc 95/5, then LiChroprep; eluent: CH₂Cl₂/EtOAc/CH₃CN 100/0/0,
10 0/100/0, 0/0/100), then crystallized from EtOAc/hexane 1/1 (30 ml), filtered off and dried, yield 0.47 g of a compound 94 having a molecular weight of 621.6 g and being represented by the formula

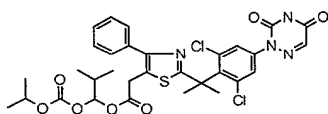


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EXAMPLE B95

A mixture of intermediate (10) (0.0078 mole) and sodium hydrocarbonate (0.0086 mole) in DMF (80 ml) was stirred for two hours at room
20 temperature. Sodium iodide (0.0086 mole) was added and a solution of 1-chloro-2-methylpropyl 1-methylethyl ester Carbonic acid (0.0086 mole) in THF (10 ml) was added dropwise. The reaction mixture was stirred overnight at 50 °C, then allowed to cool to room temperature. The reaction mixture was poured out into iced water and this mixture was extracted with EtOAc. The separated
25 organic layer was dried (MgSO₄), filtered and the solvent evaporated. The residue was purified by high-performance liquid chromatography over RP BDS Spherical (200 g Hyperprep C18 (100 Å, 8 µm; eluent: [(0.5% NH₄OAc in H₂O)/CH₃CN 90/10)]/CH₃CN (0 minute) 60/40, (24 minutes) 40/60, (up to 32 minutes) 0/100). The product fractions were collected and the solvent was
30 evaporated. The residue was dried under vacuum at 50°C, yielding 0.25 g of a

compound 95 having a molecular weight of 675.6 g and being represented by the formula

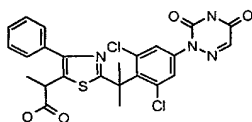


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EXAMPLES B96 and B97

A solution of the intermediate (8) (0.02 mole) and β-bromo-α methyl-γ- oxo-
Benzenebutanoic acid (0.02 mol) in ethanol (20ml) and DMF (20ml) was stirred
for four days at 70°C, then cooled and the solvent was evaporated under
reduced pressure. The residue was purified by column chromatography over
silica gel (eluent: CH₂Cl₂/EtOAc from 95/5 to 80/200). The desired fractions
were collected and the solvent was evaporated, yielding 2.2 g of a fraction A
and 8.0 g of a fraction B. The latter was purified by high-performance liquid
chromatography over RP BDS Spherical (200 g Hyperprep C18 (100 Å, 8 μm;
eluent: [(0.5% NH₄OAc in H₂O)/CH₃CN 90/10)]/CH₃CN (0 minutes) 70/30, (24
minutes) 30/70, (up to 32 minutes) 0/100). The pure fractions were collected,
the solvent was evaporated and the resulting product was recrystallized from
EtOAc, filtered off and dried, yielding 0.97 g of a compound 96 having a
molecular weight of 559.5 g and being represented by the formula

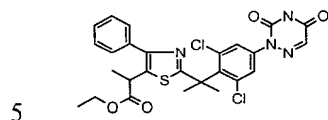
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Fraction A was purified by high-performance liquid chromatography over RP
BDS Spherical (200 g Hyperprep C18 (100 Å, 8 μm; eluent: [(0.5% NH₄OAc in
H₂O)/CH₃CN 90/10)]/CH₃CN (0 min) 65/35,(24 minutes) 65/35, (up to 32
minutes) 0/100). The pure fractions were collected, the solvent was evaporated

25

and the resulting product was recrystallized from EtOAc/hexane 1/1 (20 ml), filtered off and dried, yielding 0.33 g of a compound 97 having a molecular weight of 531.4 g and being represented by the formula



EXAMPLE B98

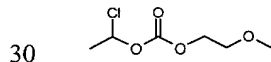
10 1,1'-carbonylbis-1H-imidazole (0.012 mole) was added at room temperature to a mixture of compound 97 (0.0088 mole) in DMF (70ml). The mixture was stirred at room temperature for one hour. Ethanol (20 ml) was added at room temperature. The mixture was stirred for two hours, then the solvent was evaporated under reduced pressure. The residue was purified by column

15 chromatography over silica gel (eluent: CH₂Cl₂/EtOH 99.5/0.5 to 95/5). The pure fractions were collected and the solvent was evaporated. The residue (3.3 g) was stirred in EtOAc/hexane 30/70. The precipitate was filtered off and dried, yielding 2.26 g (46%) of compound 96.

20 EXAMPLE B99

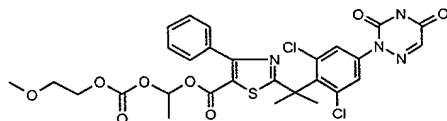
A solution of A (0.014 mole) in methylene chloride (8 ml) was added dropwise at 5°C to a solution of methoxyethanol (0.0168 mole) and pyridine (0.0182 mole) in methylene chloride (8ml) under a nitrogen flow. The mixture was stirred at 10°C for two hours, then water and methylene chloride were added

25 and the mixture was acidified with HCl 3N. The organic layer was separated, dried (MgSO₄), filtered and the solvent was evaporated, yielding 2.3 g (89%) of a compound 98 having a molecular weight of 182.6 g and being represented by the formula



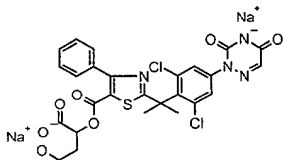
EXAMPLE B100

A solution of intermediate (13) (0.0073 mole), compound 98 (0.0109 mole), sodium hydrocarbonate (0.0073 mole) and potassium iodide (0.0073 mole) in DMF (25 ml) was stirred at 70°C for 24 hours, then brought to room temperature, poured out into ice water and acidified with HCl 3N. The precipitate was filtered, washed with water and taken up in methylene chloride. The organic layer was separated, dried (MgSO₄), filtered and the solvent was evaporated. The residue (4.6 g) was purified by column chromatography over silica gel (eluent: CH₂Cl₂/CH₃OH 99/1; 15-40µm). The pure fractions were collected and the solvent was evaporated, yielding 1.4 g (31%) of a compound 99 having a molecular weight of 649.5 g, a melting point of 88°C and being represented by the formula



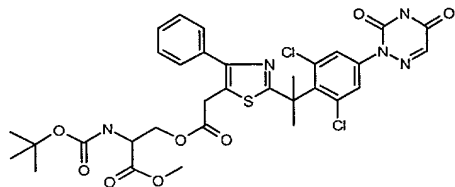
EXAMPLE B101

Sodium hydroxide 1M (0.175 ml) was added to compound 3 (0.00008716 mole) in THF (2 ml) and the reaction mixture was stirred for 30 minutes at room temperature. The resulting product was purified by reversed-phase high performance liquid chromatography. The fractions were collected and the solvent was evaporated. The aqueous concentrate was desalted on column and eluted with CH₃CN, then the product fractions were collected and the solvent was evaporated at room temperature, yielding 0.011 g (21%) of a compound 100 having a molecular weight of 649.4 g, and being represented by the formula



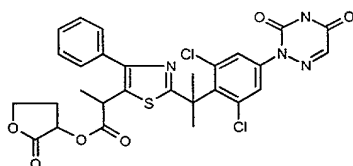
EXAMPLE B102

- 5 1,1'-carbonylbis-1H-imidazole (0.0116 mole) was added at room temperature to a stirring mixture of intermediate (10) (0.00773 mole) in methylene chloride (75ml) under a nitrogen flow. The mixture was stirred for two hours. A solution of N-[(1,1-dimethylethoxy)carbonyl]-, methyl ester L-Serine.(0.0116 mole) in methylene chloride (5 ml) was added. The mixture was stirred overnight and
- 10 then washed three times with water. The organic layer was separated, dried (MgSO_4), filtered and the solvent was evaporated. The residue (8.6 g) was purified by column chromatography over silica gel (eluent: $\text{CH}_2\text{Cl}_2/\text{THF}$ 98/2). The desired fractions were collected and the solvent was evaporated. The residue (5.4 g) was purified again by column chromatography over silica gel
- 15 (eluent: $\text{CH}_2\text{Cl}_2/\text{THF}$ 98/2). The desired fractions were collected and the solvent was evaporated. Toluene was added. The solvent was evaporated. The residue was stirred in EtOAc/DIPE 1/1 (35 ml) overnight. The precipitate was stirred in EtOAc/DIPE 1/1, filtered off, washed with EtOAc/DIPE 1/1 and DIPE, and dried in vacuo at 50°C . The residue was recrystallized from CH_3CN and
- 20 DIPE. The precipitate was filtered off, washed with CH_3CN and DIPE, and dried in vacuo at 50°C , yielding 1.72 g (31%) of a compound 101 having a molecular weight of 718.6 g and being represented by the formula



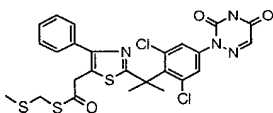
EXAMPLE B103

3-bromodihydro-2(3H)-furanone (0.0076 mole) was added dropwise at room temperature to a mixture of compound 96 (0.0038 mole) and 3-bromodihydro-2(3H)-Furanone (0.008 mole) in CH₃CN (80 ml). The mixture was stirred at 50°C overnight, then poured out into water and separated into its layers. The aqueous layer was extracted with EtOAc. The combined organic layer was dried, filtered and the solvent was evaporated under reduced pressure. The residue (2.7 g) was purified by column chromatography over silica gel (eluent: CH₂Cl₂/EtOAc 99.5/0.5 to 95/5). The pure fractions were collected and the solvent was evaporated, yielding 0.6 g of a fraction which was purified again by column chromatography over silica gel (eluent: CH₂Cl₂/EtOAc 99.5/0.5 to 95/5). The pure fractions were collected and the solvent was evaporated, yielding 0.1 g (4.3%) of a compound 102 having a molecular weight of 615.5 g and being represented by the formula



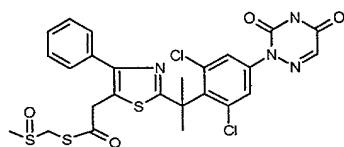
EXAMPLE B104

A solution of chloro(methylthio)- Methane (0.007 mole) in DMF (10 ml) was added dropwise to compound 74 (0.0043 mole) at room temperature. The reaction mixture was stirred overnight at room temperature, then poured out into water and extracted with EtOAc. The separated organic layer was dried, filtered and the solvent was evaporated under reduced pressure. The residue was purified by column chromatography over silica gel (eluent: CH₂Cl₂/EtOAc from 99.5/0.5 to 95/5). The desired fractions were collected and the solvent was evaporated, yielding 1.03 g of a compound 103 having a molecular weight of 593.6 g and being represented by the formula



5 EXAMPLE B105

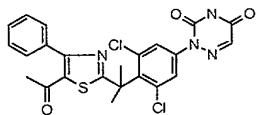
Chloro-3-benzoic acid (0.0042 mole) was added at room temperature to a mixture of compound 103 (0.0042 mole) in methylene chloride (120 ml). The mixture was stirred at room temperature overnight. The solvent was evaporated under reduced pressure. The residue was purified by column chromatography over silica gel (eluent: CH₂Cl₂/EtOAc 99.5/0.5 to 95/5). The pure fractions were collected and the solvent was evaporated. The residue was stirred in EtOAc/hexane 50/50 (20 ml). The precipitate was filtered off and dried, yielding 1.85 g (72%) of a compound 104 having a molecular weight of 609.6 g, a melting point of 154°C and being represented by the formula



EXAMPLE B106

A mixture of intermediate 8 (6.75 g) in ethanol (80 ml) and DMF (20 ml) was stirred and cooled on an ice-bath at 5°C. (2-bromo-1-phenyl-1,3-Butanedione (5.4 g) in ethanol (20 ml) was added dropwise over 30 minutes at 5°C. The reaction mixture was stirred for 30 minutes at 5°C, then for 18 hours at room temperature. The solvent was evaporated and the residue was purified by high performance liquid chromatography over silica gel (eluent: CH₂Cl₂/CH₃OH/THF 97/1/2), yielding 5 g of a first product fraction, the solvent of which was evaporated. This product fraction was stirred in DIPE, filtered off

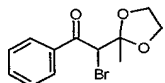
and dried, yielding 1.25 g of a compound 105 having a molecular weight of 501.4 g, a melting point of 212°C and being represented by the formula



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EXAMPLE B107

A mixture of bromine (0.0097 mole) in methylene chloride (8 ml) was added dropwise at a temperature between 10°C and 20°C to a solution of 2-(2-methyl 1,3-dioxolan-2-yl)-1-phenyl-Ethanone, (0.0097 mole) in methylene chloride (50 ml) under a nitrogen flow. The resulting mixture was stirred at 5°C for 30 minutes. A saturated NaHCO₃ solution was added. The organic layer was separated, dried (MgSO₄), filtered and the solvent was evaporated, yielding 2.7 g of a compound 106 having a molecular weight of 285.1 g and being represented by the formula



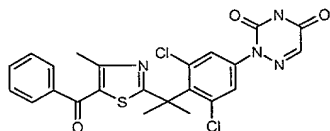
This product was used without further purification in the next example.

EXAMPLE B108

A mixture of intermediate 8 (0.0073 mole) and compound 106 (0.0095 mole) in ethanol (30 ml) and DMF (5 ml) was stirred at 80°C for 4 hours. The solvent was evaporated. The mixture was taken up in AcOEt and washed three times with H₂O/NaCl. The organic layer was separated, dried (MgSO₄), filtered and the solvent was evaporated. The residue (5 g) was purified by column chromatography over silica gel (eluent: CH₂Cl₂/CH₃OH 99/1; 15-40µm). Two fractions were collected and the solvent was evaporated. The first fraction (0.4 g) was crystallized from diethyl ether, the precipitate was filtered off and dried,

yielding 0.29 g of compound 105. The second fraction (0.44 g) was crystallized from diethyl ether, the precipitate was filtered off and dried, yielding 0.19 g of a compound 107 having a molecular weight of 501.4 g, a melting point of 174°C and being represented by the formula

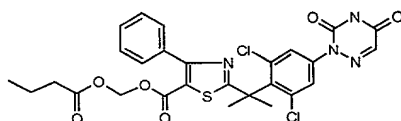
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EXAMPLE B109

A mixture of intermediate (13) (0.00496 mole), iodomethyl butyrate (0.00992 mol) and sodium hydrocarbonate (0.00496 mole) in DMF (15 ml) was stirred at 70°C for 48 hours, poured out on ice and acidified with HCl 3N until pH 4-5 was obtained. The precipitate was filtered, washed with water, taken up in methylene chloride and washed again with water. The organic layer was separated, dried (MgSO₄), filtered and the solvent was evaporated. The residue (3 g) was purified by column chromatography over silica gel (eluent: CH₂Cl₂/CH₃OH 99.5/0.5; 15-40μm). The pure fractions were collected and the solvent was evaporated. The residue (0.25 g) was crystallized from diethyl ether/DIPE. The precipitate was filtered off and dried, yielding 0.2 g (6.6%) of a compound 108 having a molecular weight of 603.5 g, a melting point of 146°C and being represented by the formula

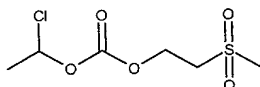
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25 EXAMPLE B110

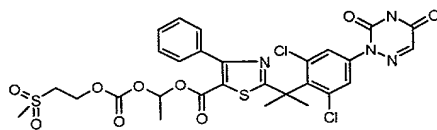
A mixture of 1-chloroethyl ester Carbonochloridic acid (0.014 mole) in methylene chloride (8 ml) was added at 5°C to a solution of 2-(methylsulfonyl)-Ethanol (0.017 mole) and pyridine (0.018 mole) in methylene chloride (8 ml)

under a nitrogen flow. The resulting mixture was stirred at 10°C for two hours and H₂O/CH₂Cl₂ was added. The mixture was acidified with HCl 3N. The organic layer was separated, dried (MgSO₄), filtered and the solvent was evaporated, yielding 2.22 g (68%) of a compound 109 having a molecular weight of 230.7 g and being represented by the formula

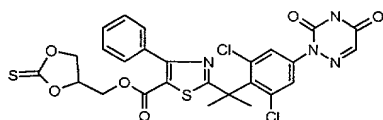


10 EXAMPLE B111

A solution of intermediate (13) (0.0054 mole), compound 109 (0.0082 mole), sodium hydrocarbonate (0.0054 mole) and potassium iodide (0.0054 mole) in DMF (20ml) was stirred at 70°C for 24 hours, brought to room temperature, poured out into ice water, acidified with HCl 3N and filtered. The precipitate was washed with water and taken up in methylene chloride. The organic layer was separated, dried (MgSO₄), filtered and the solvent was evaporated. The residue (3.5 g) was purified by column chromatography over silica gel (eluent: CH₂Cl₂/CH₃OH 99/1; 15-40µm). The pure fractions were collected and the solvent was evaporated, yielding 0.6 g (16%) of a compound 110 having a molecular weight of 697.6 g, a melting point of 104°C and being represented by the formula



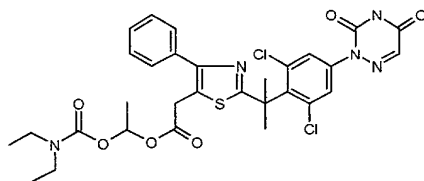
brought to room temperature. 4-(hydroxymethyl) 1,3-Dioxolane-2-thione (0.006 mole) was added. The mixture was stirred at room temperature for 60 hours, poured out into water and acidified with HCl 3N. The precipitate was filtered, washed with water, taken up in EtOAc and washed again twice with water. The organic layer was separated, dried (MgSO₄), filtered and the solvent was evaporated. The residue (2.08 g) was purified by column chromatography over silica gel (eluent: CH₂Cl₂/CH₃OH 99/1; 15-40μm). The pure fractions were collected and the solvent was evaporated. The residue was crystallized from diethyl ether, the precipitate was filtered off and dried, yielding 0.35g of a compound 111 having a molecular weight of 619.5 g, a melting point of 130°C and being represented by the formula



EXAMPLE B113

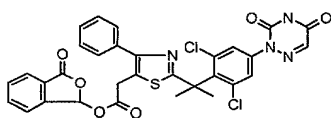
A mixture of intermediate (10) (0.0039 mole) and diethyl-, 1-chloroethyl ester Carbamic acid (0.0039 mole) in CH₃CN (40 ml) was stirred at 60°C.

Triethylamine (0.0039 mole) was added. The reaction mixture was stirred for 24 hours. The solvent was evaporated. The residue was purified by flash chromatography over silica gel (eluent: CH₂Cl₂/CH₃OH 99.7/0.3). The desired fractions were collected and the solvent was evaporated till dryness. The residue was stirred in hexane, the precipitate was filtered off, washed and dried under vacuum at 50°C, yielding 0.4 g of a compound 112 having a molecular weight of 660.6 g and being represented by the formula



EXAMPLE B114

1,1'-carbonylbis-1H-imidazole (0.0084 mole) was added to a solution of
intermediate (10) (0.0056 mole) in DMF (30 ml). The reaction mixture was
5 stirred for one hour at room temperature. C (0.0112 mol) was added. Then
(0.0056 mol) was added at room temperature and the resulting reaction mixture
was stirred for two hours at room temperature. The reaction mixture was
poured out into water and the aqueous layer was extracted with EtOAc. The
10 organic layer was separated, dried, filtered and the solvent evaporated under
reduced pressure. The residue was purified by column chromatography over
silica gel (eluent: CH₂Cl₂/EtOAc 99.5/0.5 up to 96/4). The product fractions
were collected and the solvent was evaporated under reduced pressure. The
residue was dried under vacuum, yielding 0.95 g of a fraction which was dried
15 undervacuum at 70°C for two days, yielding 0.78 g (21%) of a compound 113
having a molecular weight of 649.5 g and being represented by the formula

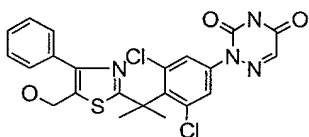


EXAMPLE B115

A mixture of published as EP98203148.6 (0.0085 mole) in THF (70 ml)
was added dropwise at 0°C to a suspension of lithium aluminum hydride
(0.0085 mole) in THF (10 ml) under a nitrogen flow. The mixture was stirred at
a temperature between 5°C and 15°C for three hours. Water and EtOAc were
25 added. The mixture was acidified with HCl 3N. The organic layer was
separated, dried (MgSO₄), filtered and the solvent was evaporated. The
residue (8.9 g) was purified by column chromatography over silica gel (eluent:

CH₂Cl₂/CH₃OH 98/2; 15-35 μm). The pure fractions were collected and the solvent was evaporated. The residue was crystallized from CH₃CN. The precipitate was filtered off and dried, yielding 0.44 g of a compound 114 having a molecular weight of 489.4 g and being represented by the formula

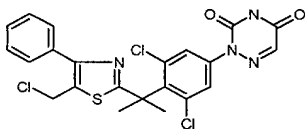
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EXAMPLE B116

Thionyl chloride (0.0049 mole) was added at room temperature to a mixture of compound 114 (0.0033 mole) in methylene chloride (120 ml). The mixture was stirred at room temperature for two hours and washed with NaHCO₃ (saturated). The organic layer was separated, dried (MgSO₄), filtered and the solvent was evaporated, yielding 1.7 g (100%) of a compound 115 having a molecular weight of 507.8 g and being represented by the formula

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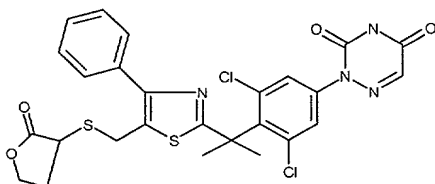
EXAMPLE B117

A mixture of compound 115 (0.0033 mole), dihydro-3-mercapto- 2(3H)-Furanone (0.0065 mole) and potassium carbonate (0.0065 mole) in CH₃CN (70 ml) and DMF (5 ml) was stirred at 90°C for two hours, brought to room temperature, evaporated, taken up in water, acidified with HCl 3N, extracted with EtOAc and washed with water. The organic layer was separated, dried (MgSO₄), filtered and the solvent was evaporated. The residue was purified by column chromatography over silica gel (eluent: CH₂Cl₂/CH₃OH 99/1; 15-40 μm). One fraction was collected and, after evaporation of the solvent, taken up in DIPE and filtered, yielding 0.43 g of a compound 116 having a molecular

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weight of 589.5 g, a melting point of 100°C and being represented by the formula

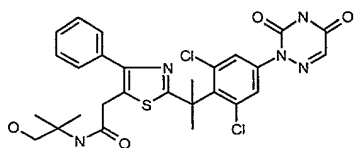


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EXAMPLE B118

1,1'-carbonylbis-1H-imidazole (0.941 g) was added to a suspension of intermediate (10) (0.00387 mole) in methylene chloride (40 ml) and stirred at room temperature. The mixture was stirred for one hour at room temperature.

10 Methyl-2-amino-2-propanol (0.0058 mole) was added and the reaction mixture was stirred overnight at room temperature. The reaction mixture was washed with water. The layers were separated. The organic layer was dried (MgSO₄), filtered and the solvent was evaporated under reduced pressure. The residue was purified by column chromatography over silica gel (eluent: CH₂Cl₂/EtOAc 15 99/1 to 95/5). The pure fractions were collected and the solvent was evaporated, resulting in a fraction which was stirred in EtOAc. The precipitate was filtered off and dried, yielding 0.5 g (22%) of a compound 117 having a molecular weight of 588.5 g and being represented by the formula



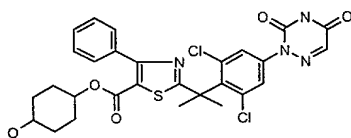
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EXAMPLE B119

A mixture of intermediate (13) (0.003 mole) and 1,1'-carbonylbis-1H-imidazole (0.045 mole) in DMF (15 ml) was stirred at 40°C for one hour. 1,4-cyclohexanediol (0.015 mole) was added then a solution of 1,8-

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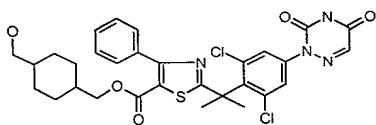
diazabicyclo (5.4.0) undecene-7 (0.003 mole) in DMF (3 ml). The mixture was stirred at 40°C for two hours, poured out into water, acidified with HCl 3N, extracted with EtOAc and washed with water. The organic layer was separated, dried (MgSO₄), filtered and the solvent was evaporated. The residue was purified by column chromatography over silica gel (eluent: CH₂Cl₂/CH₃OH 96/4; 15-40 μm). The pure fractions were collected and the solvent was evaporated, yielding 0.86 g (47%) of a compound 118 having a molecular weight of 601.5 g and being represented by the formula



Further analysis shows that it consists of a mixture of 35% of an isomer with a melting point of 141°C and 65% of another isomer with a melting point of 128°C.

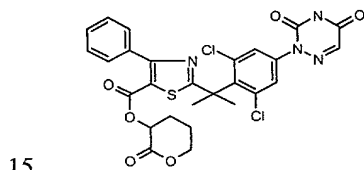
EXAMPLE B120

A mixture of intermediate (13) (0.0018 mole) and 1,1'-carbonylbis-1H-imidazole (0.0023 mole) in DMF (8 ml) was stirred at 40°C for one hour. A solution of 1,4-di(hydroxymethyl) cyclohexane (0.0089 mole) and 1,8-diazabicyclo (5.4.0) undecene-7 (0.0018 mole) in DMF (3 ml) was added. The mixture was stirred at 60°C for two hours, brought to room temperature and water was added. The mixture was acidified with HCl 3N, filtered and the precipitate was washed with water, taken up in EtOAc and washed with water. The organic layer was separated, dried (MgSO₄), filtered and the solvent was evaporated. The residue was purified by column chromatography over silica gel (eluent: CH₂Cl₂/CH₃OH 98/2; 15-40 μm). The pure fractions were collected and the solvent evaporated, yielding a fraction which was crystallized from diethyl ether/CH₃CN. The precipitate was filtered off and dried, yielding 0.282 g of a compound 119 having a molecular weight of 629.6 g and being represented by the formula



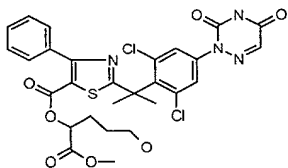
5 EXAMPLE B121

A mixture of intermediate (13) (0.0028 mole), tetrahydro-3-iodo-2*H*-Pyran-2-one (0.0056 mole) and sodium hydrocarbonate (0.0028 mole) in DMF (10 ml) was stirred at 70°C for two hours, brought to room temperature, poured out into water and acidified. The precipitate was filtered, washed with water, taken up in
10 EtOAc and washed with water. The organic layer was separated, dried (MgSO₄), filtered and the solvent was evaporated, yielding 2.44 g of a compound 120 having a molecular weight of 601.5 g and being represented by the formula



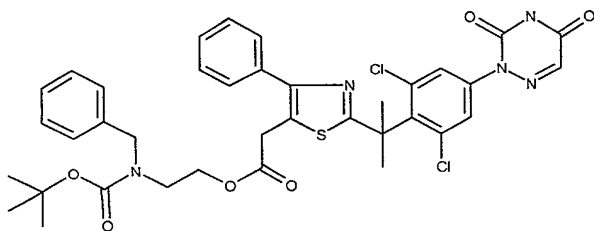
15 EXAMPLE B122

Compound 120 (0.0028 mole) was chromatographed over 300 g of silica (eluent: CH₂Cl₂/CH₃OH 99/1). One fraction was collected and, after
20 evaporating the solvent, was purified by column chromatography over Kromasil (eluent: CH₃CN/AcNH₄ 65/35). One fraction was collected and, after evaporating the solvent, was taken up in pentane and filtered, yielding 0.061 g of a compound 121 having a molecular weight of 633.5 g, a melting point of
25 100°C and being represented by the formula



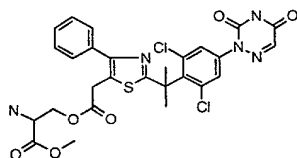
EXAMPLE B123

5 1,1'-carbonylbis-1H-imidazole (0.0116 mole) was added at room temperature under a nitrogen flow to a stirring mixture of intermediate (10) (0.00773 mole) in methylene chloride (75 ml). The mixture was stirred for three hours. A solution of (2-hydroxyethyl)(phenylmethyl)-1,1-dimethylethyl ester Carbamic acid, (0.0116 mole) in methylene chloride (5 ml) was added. The
10 mixture was stirred overnight and then washed three times with water. The organic layer was separated, dried (MgSO_4), filtered and the solvent was evaporated. The residue was purified by column chromatography over silica gel (eluent: $\text{CH}_2\text{Cl}_2/\text{THF}$ 98/2). The desired fractions were collected and the solvent was evaporated. Toluene was added, then the solvent was evaporated. The
15 residue was purified again by high performance liquid chromatography over Hyperprep (eluent: (0.5% ammonium acetate aqueous solution/ CH_3CN 90/10)/ CH_3CN 40/60 and 3/97; column: C18 HS BDS 100 Å 8 μm). The desired fractions were collected and the solvent was evaporated. The residue was dissolved in $\text{CH}_2\text{Cl}_2/\text{EtOAc}$, filtered over a paper-frit and the filtrate was
20 evaporated. The residue was stirred in hexane overnight. The precipitate was filtered off, washed with hexane and dried in vacuo at 50°C, yielding 3.2 g of a compound 122 having a molecular weight of 633.5 g and being represented by the formula



EXAMPLE B124

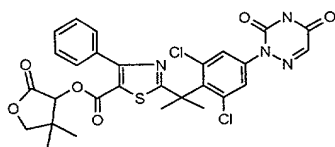
Trifluoroacetic acid (3 ml) was added to a solution of compound 101 (0.00122 mole) in methylene chloride (10 ml) and stirred at room temperature under a nitrogen flow for three hours. The solvent was evaporated, then toluene was added and the solvent was again evaporated. The residue was stirred in methylene chloride (15 ml). The mixture was treated with gaseous hydrogen chloride for 15 minutes. Some toluene was added, then all solvent was evaporated again. The resultant oil was stirred in 2-propanone, decanted, then after standing for two days under a nitrogen atmosphere, the mixture was stirred overnight in DIPE, filtered off, washed and dried under vacuum at 50°C, yielding 0.34 g of a compound 123 having a molecular weight of 655.0 g and being represented by the formula



EXAMPLE B125

A mixture of intermediate (13) (0.0024 mole) and 1,1'-carbonylbis-1H-imidazole (0.0031 mole) in DMF (8 ml) was stirred at 40°C for one hour. A mixture of dihydro-3-hydroxy-4,4-dimethyl-2(3H)-Furanone (0.0048 mole) and 1,8-diazabicyclo (5.4.0) undecene-7 (0.0024 mole) in DMF (1 ml) was added. The mixture was stirred at 40°C for two hours, brought to room temperature, poured out into HCl 1N and filtered. The precipitate was washed with water, taken up in EtOAc and washed with water. The organic layer was separated, dried (MgSO₄), filtered and the solvent was evaporated. The residue was crystallized from diethyl ether/CH₃CN. The precipitate was filtered off and dried, yielding 0.78 g (53%) of the (R) isomer (having an optical rotation, measured in

DMF, of + 16.23°) of a compound 124 having a molecular weight of 615.5 g, a melting point of 248°C and being represented by the formula

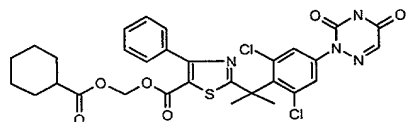


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EXAMPLE B126

A mixture of intermediate (13) (0.0029 mole), chloromethyl cyclohexane carboxylate (0.0058 mole), sodium hydrocarbonate (0.0029 mole) and potassium iodide (0.0029 mole) in DMF (10 ml) was stirred at 70°C for 12 hours, brought to room temperature and HCl 1N was added. The mixture was filtered, the insoluble was taken up in EtOAc and washed with water. The organic layer was separated, dried (MgSO₄), filtered and the solvent was evaporated. The residue was purified by column chromatography over silica gel (eluent: CH₂Cl₂/CH₃OH 99/1; 15-40µm). One fraction was collected and, after evaporating the solvent, was crystallized from diethyl ether. The precipitate was filtered off and dried, yielding 0.5 g of a compound 125 having a molecular weight of 643.5 g, a melting point of 130°C and being represented by the formula

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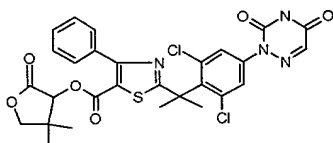


EXAMPLE B127

A mixture of intermediate (13) (0.00278 mole) and 1,1'-carbonylbis-1H-imidazole (0.0036 mole) in DMF (9 ml) was stirred at 40°C for one hour. A solution of (-)-(D) dihydro-3-hydroxy-4,4-dimethyl-2(3H)Furanone (0.00556 mole) and 1,8-diazabicyclo (5.4.0) undecene-7 (0.00278 mole) in DMF (1 ml)

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was added. The mixture was stirred at 40°C for two hours, then brought to room temperature. HCl 1N was added. The precipitate was filtered, washed with water, taken up in EtOAc and washed again with water. The organic layer was separated, dried (MgSO₄), filtered and the solvent was evaporated. The residue was purified by column chromatography over silica gel (eluent: CH₂Cl₂/CH₃OH 99/1; 35-70µm). The pure fractions were collected and the solvent was evaporated. The residue was crystallized from diethyl ether/CH₃CN. The precipitate was filtered off and dried, yielding 1.15 g (68%) of the (S) isomer (having an optical rotation, measured in DMF, of -11.84°) of a compound 126 having a molecular weight of 615.5 g, a melting point of 244°C and being represented by the formula



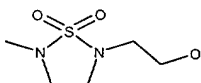
EXAMPLE B128

Compound 97 (0.027 mole) was separated by chiral column chromatography over Chiralpak AD (500 g) (eluent: hexane/ethanol + 1% trifluoroacetic acid 70/30). Two fractions were collected and, after evaporating the solvent, gave two 0.7 g oils which were treated with a saturated aqueous sodium hydrocarbonate solution. This mixture was extracted with methylene chloride, and co-evaporated with EtOAc. The residue was stirred in DIPE, washed with DIPE, and dried overnight under vacuum at 50°C, yielding 0.5 g of a first enantiomer (having an optical rotation, measured in methanol, of -63.95°) and 0.5 g of a second enantiomer (having an optical rotation, measured in methanol, of + 61.36°).

EXAMPLE B129

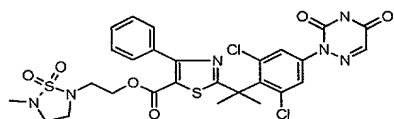
A mixture of 2-methyl-, 1,1-dioxide-1,2,5-Thiadiazolidin (0.014 mole), bromo-2-ethanol (0.028 mole) and potassium carbonate (0.0167 mole) in CH₃CN (15 ml)

was stirred at 80°C for 60 hours and bromo-2-ethanol (0.014 mole) was further added. The mixture was stirred and refluxed for 12 hours and bromo-2-ethanol (0.014 mole) was further added. The mixture was stirred and refluxed for 12 hours, brought to room temperature and filtered. The precipitate was washed with methylene chloride and the mixture was evaporated. The residue was purified by column chromatography over silica gel (eluent: CH₂Cl₂/CH₃OH; 98/2 35-70µm). One fraction was collected and the solvent was evaporated, yielding 0.91 g of a compound 127 having a molecular weight of 180.2 g and being represented by the formula



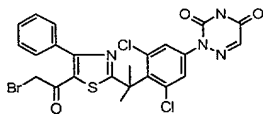
EXAMPLE B130

A mixture of intermediate (13) (0.0024 mole) and 1,1'-carbonylbis-1H-imidazole (0.0031 mole) in DMF (6 ml) was stirred at 40°C for one hour. A solution of compound 127 (0.0029 mole) and 1,8-diazabicyclo (5.4.0) undecene-7 (0.0024 mole) in DMF (1 ml) was added. The mixture was stirred at 40°C for four hours, brought to room temperature and ice water was added. The mixture was acidified with HCl 3N and filtered. The precipitate was washed with water, taken up in methylene chloride and washed with water. The organic layer was separated, dried (MgSO₄), filtered and the solvent was evaporated. The residue was purified by column chromatography over silica gel (eluent: CH₂Cl₂/CH₃OH 99/1; 15-40µm). One fraction was collected and, after evaporation of the solvent, was taken up in diethyl ether and filtered, yielding 0.43 g (26%) of a compound 128 having a molecular weight of 665.6 g, a melting point of 112°C and being represented by the formula



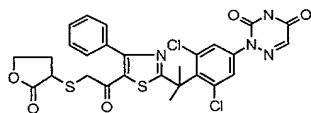
EXAMPLE B131

A solution of compound 105 (0.0030 mole) in THF (10 ml) was stirred at room temperature. A solution of B (0.0028 mol) in THF (10 ml) was added slowly and dropwise. The reaction mixture was stirred for two and a half hours at room temperature. The precipitate was filtered off, washed with THF and the filtrate was evaporated under reduced pressure. The residue was dissolved in methylene chloride, washed with water, dried (MgSO_4), filtered and the solvent was evaporated, yielding 1.7 g of a compound 129 having a molecular weight of 580.3 g and being represented by the formula



EXAMPLE B132

A mixture of compound 129 (0.003 mole), dihydro-3-mercapto-2(3H)-Furanone (0.006 mole) and potassium carbonate (0.006 mole) in CH₃CN (20 ml) and DMF (3 ml) was stirred for 90 minutes at 90°C. The mixture was allowed to cool to room temperature. The reaction was quenched with water (25 ml) and extracted twice with EtOAc. The separated organic layer was dried (MgSO₄), filtered and the solvent evaporated. The residue was purified by flash column chromatography over silica gel (eluent: CH₂Cl₂/CH₃OH 99.8/0.2). The desired fractions were collected and the solvent was evaporated. The residue was purified by high performance liquid chromatography over silica gel (eluent: CH₂Cl₂/CH₃OH from 100/0 to 50/50). The product fractions were collected and the solvent was evaporated. The residue was stirred in DIPE, filtered off, washed and dried under vacuum at 50°C, yielding 0.35 g of a compound 130 having a molecular weight of 617.5 g and being represented by the formula



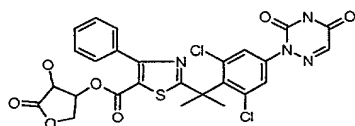
5 EXAMPLE B133

A mixture of intermediate (13) (0.004 mole) and 1,1'-carbonylbis-1H-imidazole (0.0052 mole) in DMF (13 ml) was stirred at 40°C for one hour. A solution of dihydro-3,4-dihydroxy-, (3R,4R)-2(3H)-furanone (0.008 mole) and 1,8-diazabicyclo (5.4.0) undecene-7 (0.004 mole) in DMF (2 ml) was added.

10 The mixture was stirred at 40°C for five hours then at room temperature overnight and HCl 0.5N was added. The mixture was filtered and the precipitate was washed with water, taken up in EtOAc and washed with water. The organic layer was separated, dried (MgSO₄), filtered and the solvent was evaporated. The residue was purified by column chromatography over silica gel

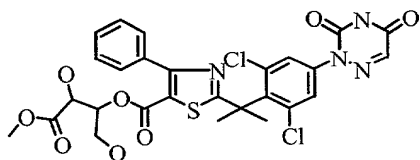
15 (eluent: CH₂Cl₂/CH₃OH 97/3; 15-40μm). Two fractions were collected and the solvent was evaporated. The first fraction (0.25 g) was taken up in DIPE and filtered, yielding 0.2 g of a compound 131 having a molecular weight of 603.4 g, a melting point of 144°C, an optical rotation (measured in methanol) of -44.95° and being represented by the formula

20



The second fraction consists of 0.3 g of a compound 132 having a

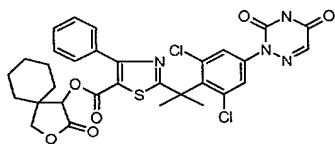
25 molecular weight of 635.5 g, a melting point of 110°C, an optical rotation (measured in methanol) of -14.8° and being represented by the formula



5 EXAMPLE B134

1,1'-carbonylbis-1H-imidazole (0.0027 mole) was added to a solution of intermediate (13) (0.0021 mole) in DMF (10 ml). The mixture was stirred at 40°C for one hour and 1-(hydromethyl)-,γ-lactone Cyclohexaneglycolic acid (0.0032 mole) then 1,8-diazabicyclo (5.4.0) undecene-7 (0.0021 mole) were added. The mixture was stirred at 40°C for 12 hours, poured out into ice water and acidified with HCl 3N. The precipitate was filtered and washed with water. The mixture was dried, taken up in methylene chloride and washed with water. The organic layer was separated, dried (MgSO₄), filtered and the solvent was evaporated. The residue was purified by column chromatography over silica gel (eluent:CH₂Cl₂/CH₃OH 99/1; 15-40μm). The pure fractions were collected and the solvent was evaporated, giving 0.6 g of a fraction which was crystallized from CH₃CN/diethyl ether. The precipitate was filtered off and dried, yielding 0.31 g (22%) of a compound 133 having a molecular weight of 655.6 g and being represented by the formula.

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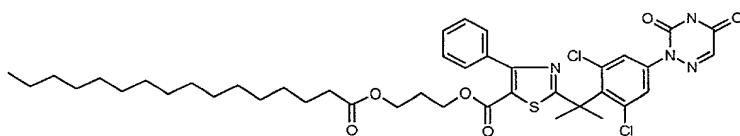


EXAMPLE B135

Hexadecanoic acid chloride (0.002 mole) was added slowly at 0°C to a solution of compound 65 (0.002 mole) and triethylamine (0.003 mole) in methylene chloride (20 ml). The mixture was stirred at room temperature for

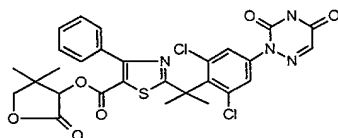
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five hours and poured out into water. The organic layer was separated, dried (MgSO₄), filtered and the solvent was evaporated. The residue (1.9 g) was purified by column chromatography over silica gel (eluent: CH₂Cl₂/CH₃OH 99.5/0.5;15-40μm). Two fractions were collected and after evaporation of the solvent, were crystallized from DIPE. The precipitate was filtered off and dried, yielding 0.27 g (17%) of a compound 134 having a molecular weight of 799.9 g and being represented by the formula



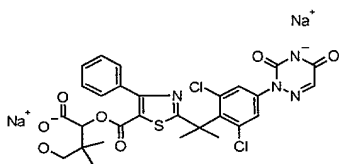
EXAMPLE B136

A mixture of intermediate (13) (0.006 mole) and 1,1'-carbonylbis-1H-imidazole (0.0077 mole) in DMF (25ml) was stirred at 40°C for one hour. A solution of dihydro-3-hydroxy-4,4-dimethyl-2(3H)-Furanone (0.012 mole) and 1,8-diazabicyclo (5.4.0) undecene-7 (0.006 mole) in DMF (5 ml) was added. The mixture was stirred at 40°C for three hours, then brought to room temperature, poured out into HCl 1N, filtered, taken up in EtOAc and washed with water. The organic layer was separated, dried (MgSO₄), filtered and the solvent was evaporated. The residue (8.9 g) was purified by column chromatography over silica gel (eluent: CH₂Cl₂/CH₃OH 99/1;15-35μm). The pure fractions were collected and the solvent was evaporated. The residue was crystallized from diethyl ether/CH₃CN. The precipitate was filtered off and dried, yielding 2.3 g of a compound 135 having a molecular weight of 615.5 g and being represented by the formula



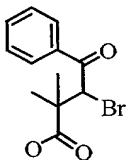
EXAMPLE B137

Sodium hydroxide 1M (0.000328 mole) was added to compound 135 (0.000164 mole) in THF (4 ml) and the reaction mixture was stirred overnight at room temperature. The resulting product was purified by high performance liquid chromatography over Hyperprep RP-C18 BDS (eluent: 0.5% ammonium acetate aqueous solution/CH₃CN 90/10/CH₃CN 90/10). The product fractions were collected and the organic solvent was evaporated. The aqueous concentrate was desalted on column and eluted with CH₃CN. The product fractions were collected and the solvent was evaporated at room temperature, yielding 0.045 g (41%) of a compound 136 having a molecular weight of 677.5 g and being represented by the formula



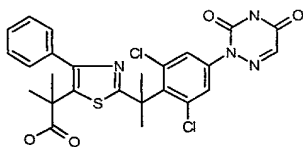
EXAMPLE B138

Bromine (two drops) was added at room temperature to a solution of α,α -dimethyl- γ -oxo-Benzenebutanoic acid (0.01 mole) in methylene chloride (10ml) and acetic acid (2 ml). A hydrogen bromide/acetic acid mixture (1 drop) was added. Bromine (0.0105 mole) was further added at room temperature to the mixture, which was stirred at room temperature for one hour. Nitrogen was bubbled through the mixture for one hour. The solvent was evaporated under reduced pressure. The residue was co-evaporated with toluene, yielding 2.7 g (95%) of a compound 137 having a molecular weight of 285.1 g and being represented by the formula



EXAMPLE B139

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204120" 92854001
A mixture of intermediate (8) (0.05 mole) and compound 137 (0.05 mole) in
5 ethanol (150 ml) and DMF (50 ml) was stirred for 72 hours at 70°C, yielding a
fraction which was poured out into water and then separated into its layers. The
aqueous layer was extracted with EtOAc. The combined organic layer was
washed with water, dried, filtered and the solvent was evaporated under
reduced pressure. The residue was crystallized from CH₃CN. The precipitate
10 was filtered off and dried, giving a product which was crystallized again from
CH₃CN. The precipitate was filtered off and dried, yielding 8.73 g of a
compound 138 having a molecular weight of 545.5 g and being represented by
the formula



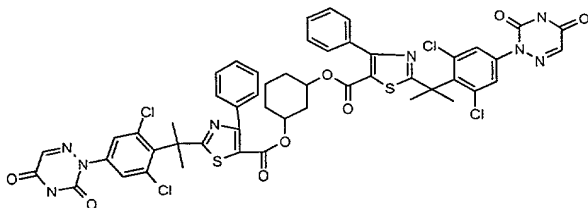
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EXAMPLE B140

1,1'-carbonylbis-1H-imidazole (0.0042 mole) was added to a solution of
20 intermediate (13) (0.0034 mole) in DMF (10 ml). The mixture was stirred at
40°C for one hour. 1,3-dihydroxy cyclohexane (0.02 mole) then 1,8-
diazabicyclo (5.4.0) undecene-7 (0.0034 mole) were added. The mixture was
stirred at 40°C for six hours, poured out into ice water and acidified with HCl
3N. The precipitate was filtered, washed with water, dried, taken up in
25 methylene chloride and washed with water. The organic layer was separated,
dried (MgSO₄), filtered and the solvent was evaporated. The residue was
purified by column chromatography over silica gel (eluent: CH₂Cl₂/CH₃OH

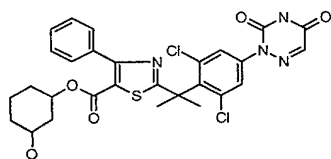
98/2;15-40 μ m). The pure fractions were collected and the solvent was evaporated, yielding 0.14 g (2.5%) of the cis-isomer of a compound 139 having a molecular weight of 1086.9 g and a melting point of 180°C and being represented by the formula

5



and 1.4 g of a fraction which was then crystallized from 2-propanone/diethyl ether. The precipitate was filtered off and dried, yielding 1 g (49%) of a compound 140 having a molecular weight of 601.5 g and a melting point of 175°C and being represented by the formula

10

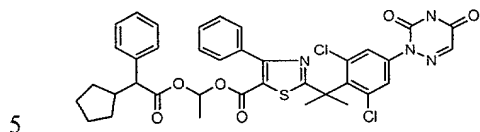


15 EXAMPLE B141

A mixture of intermediate (13) (0.0037 mole), α -cyclopentyl-, 1-chloroethyl ester Benzeneacetic acid (0.00733 mole), sodium hydrocarbonate (0.0037 mole) and potassium iodide (0.0037 mole) in DMF (10 ml) was stirred at 70°C for 2 days, brought to room temperature. HCl 1N was added. The precipitate was taken up in EtOAc and washed with water. The organic layer was separated, dried (MgSO₄), filtered, and the solvent was evaporated. The residue was purified by column chromatography over silica gel (eluent: CH₂Cl₂/CH₃OH; 99/1;15-40 μ m). The pure fractions were collected and the solvent was evaporated. The residue was purified by high-performance liquid chromatography over Kromacil C-18 (eluent: 5% ammonium acetate aqueous solution/CH₃CN 20/80). The pure fractions were collected and the solvent was

25

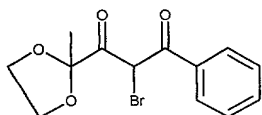
evaporated, yielding 0.69 g (25%) of a compound 141 having a molecular weight of 733.7 g and a melting point of 110°C and being represented by the formula



EXAMPLE B142

10 A mixture of N,N,N-trimethyl- (tribromide) Benzenaminium (0.005 mole) in THF (25 ml) was stirred at room temperature. Phenyl trimethylammonium bromide (0.005 mole) was added portionwise at room temperature for one hour. Water was added, then the mixture was extracted with methylene chloride. The organic layer was separated, dried, filtered and the solvent was evaporated, yielding 1.55 g (100%) of a compound 142 having a molecular weight of 313.1 g and being represented by the formula

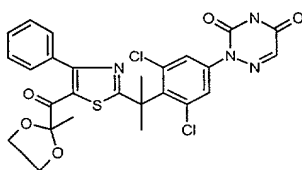
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20 EXAMPLE B143

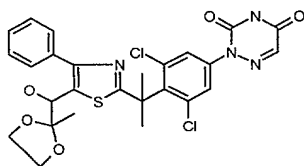
A mixture of intermediate (8) (0.0045 mole) and compound 142 (0.005 mole) in ethanol (20 ml) and DMF (10 ml) was stirred at 60°C for two hours. The solvent was evaporated. The residue was purified by flash column chromatography over silica gel (eluent: CH₂Cl₂/CH₃OH 99.7/0.3). The pure fractions were collected and the solvent was evaporated, giving a fraction which was stirred in ethanol (10 ml). The resulting precipitate was filtered off, washed with DIPE and dried, yielding 0.4 g of a compound 143 having a molecular weight of 573.5 g and being represented by the formula

25



5 EXAMPLE B144

A mixture of compound 143 (0.0094 mole) in methanol (50 ml) was stirred at room temperature. Sodium borohydride (0.01 mole) was added portionwise over 30 minutes. The mixture was stirred for 90 minutes. More sodium borohydride (0.014 mole) was added portionwise over 30 minutes and the
10 resulting mixture was further stirred for 90 minutes. The resulting precipitate was filtered off, washed with methanol and DIPE and dried, yielding 4.5 g of a compound 144 having a molecular weight of 575.5 g and being represented by the formula



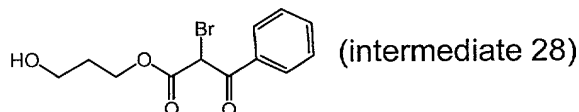
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Example B145

a) A solution of β -oxo-3-hydroxypropyl benzenepropanoic acid ester (0.097 mol; 26.0 g with 83% purity) in chloroform (250 ml) was stirred vigorously at
20 room temperature under nitrogen atmosphere. N-bromosuccinimide (0.1 mol) was added portionwise over 2 hours. The reaction mixture was stirred for one hour at room temperature. More N-bromosuccinimide (2.5 g) was added and the reaction mixture was stirred for 1.5 hours at room temperature. An aqueous NaHCO_3 solution (16.8 g NaHCO_3 in 200 ml of water) was added and stirring
25 was continued for 5 minutes. The layers were separated. The organic layer

was dried, filtered and the solvent evaporated, then co-evaporated with toluene,

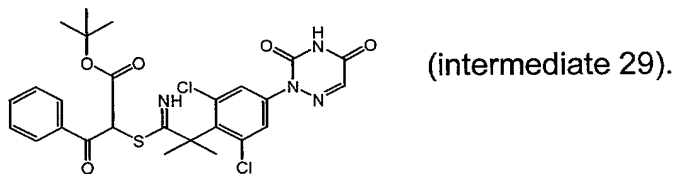
yielding 35.9 g of



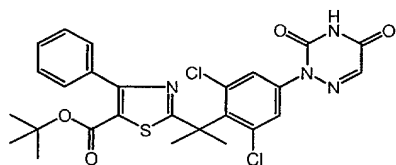
b) A mixture of intermediate (8) (0.00457 mol), intermediate (28) (0.00503 mol) and DMF (0.00457 mol) in 1,3-propanediol (10 ml) was stirred at 70°C for 6 hours, then cooled and poured out into ice water. The precipitate was filtered, washed with HCl diluted/H₂O and dried. The residue was taken up in CH₂Cl₂. The organic layer was separated, washed with H₂O, dried, filtered and the solvent was evaporated. The residue was purified by column chromatography over silica gel (eluent: CH₂Cl₂/CH₃OH 97.5/2.5; 15-40µm). The pure fractions were collected and the solvent was evaporated. The residue was crystallized from DIPE. The precipitate was filtered off and dried, yielding 0.55g of 3-hydroxypropyl 2-[1-[2,6-dichloro-4-(4,5-dihydro-3,5-dioxo-1,2,4-triazin-2(3H)-yl)phenyl]-1-methylethyl]-4-phenyl-5-thiazolecarboxylate (compound 145).

Example B146

a) A mixture of intermediate (8) (0.0119 mol), (±)-1,1-dimethylethyl α-bromo-beta-oxo-benzenepropanoate (0.0137 mol) and K₂CO₃ (0.0357 mol) in acetonitrile (55 ml) was stirred at room temperature for 3.5 hours. Ice and ethyl acetate were added. The mixture was acidified with HCl 3N. The organic layer was separated, dried, filtered and the solvent was evaporated. The product was used without further purification, yielding 8 g of



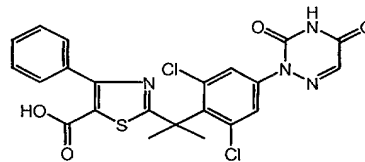
b) Intermediate (29) (0.0119 mol) and *tert*-butanol (24 g) were stirred and refluxed for 2 hours. The mixture was brought to room temperature. The solvent was evaporated. The residue was taken up in dichloromethane. The organic solution was washed with water, dried, filtered and the solvent was evaporated. The residue was purified by column chromatography over silica gel (eluent : CH₂Cl₂/CH₃OH 99/1). The pure fractions were collected and the solvent was evaporated, yielding 0.45g of,



(intermediate 30 , mp. 130°C).

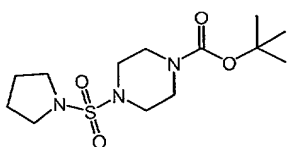
c) A mixture of intermediate (30) (0.0518 mol) in trifluoroacetic acid (200 ml) was stirred at room temperature for 4 hours and poured out on ice. The precipitate was filtered, washed with water and dried. The residue was taken up in dichloromethane. The organic layer was separated, washed with water, dried, filtered and the solvent was evaporated. The residue was purified by column chromatography over silica gel (eluent : CH₂Cl₂/CH₃OH/acetic acid; 97/3/0.1). The pure fractions were collected and the solvent was evaporated. The residue was crystallized from acetonitrile. The precipitate

was filtered off and dried, yielding 27.1 g of

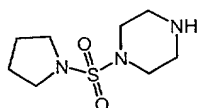


(intermediate 31, mp. >250°C).

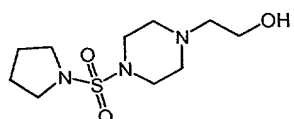
d) A solution of 1-chlorosulfonylpyrrolidine (0.0088 mol) in dichloromethane (5ml) was added dropwise at room temperature to a mixture of 1,1-dimethylethyl 1-piperazinecarboxylate (0.0088 mol) and triethylamine (0.0177 mol) in dichloromethane (15 ml). The mixture was stirred at room temperature for 12 hours and HCl 0.5N was added. The mixture was separated and extracted with dichloromethane. The dichloromethane layer were brought together, dried, filtered and the solvent was evaporated, yielding

2.8 g of  (intermediate 32).

e) A mixture of intermediate (32) (0.088 mol) and a mixture of HCl (5N) in isopropanol (0.0263 mol) in isopropanol (30 ml) was stirred and refluxed for 5 hours, evaporated, taken up in DIPE, filtered and dried, yielding

2g of  (intermediate 33).
Hydrochloride (1:1)

- 5 f) A mixture of intermediate (33) (0.0078 mol), 1-bromo-2-ethanol (0.0313 mol) and Na_2CO_3 (0.047 mol) in ethanol (45 ml) was stirred at 80°C for 18 hours, brought to room temperature and water was added. The mixture was extracted twice with dichloromethane. The organic layer was separated, dried, filtered and the solvent was evaporated, yielding 2 g of

 (intermediate 34).

10

- g) Intermediate (31) (0.003 mol) and 1,1'-carbonylbis-1*H*-imidazole (CDI) (0.0037 mol) were stirred at 40°C for 1 hour and a solution of intermediate (34) (0.0051 mol) and 1,8-diaza-7-bicyclo[5.4.0]undecene (DBU) (0.003 mol) in DMF (15ml) was added. The mixture was stirred at 40°C for 6 hours, brought to
15 room temperature, poured out into ice water, acidified with HCl 3N and filtered. The precipitate was washed with water, taken up in dichloromethane and washed with water. The organic layer was separated, dried, filtered and dried. The residue was purified by column chromatography over silica gel (eluent : $\text{CH}_2\text{Cl}_2/\text{CH}_3\text{OH}$ 98/2), yielding 0.775 g of,



a) Bromine (2 drops) was added at room temperature to a solution of 3-benzoyl-2,2-dimethyl-propionic acid (0.01 mol) in dichloromethane (10 ml) and acetic acid (2 ml). A mixture of HBr in acetic acid (1 drop) was added. Bromine (0.0105 mol) was added further at room temperature to the mixture. The mixture was stirred at room temperature for 1 hour. Nitrogen gas was bubbled through the mixture for 1 hour. The solvent was evaporated under reduced pressure. The residue was co-evaporated with toluene, yielding 2.7 g of

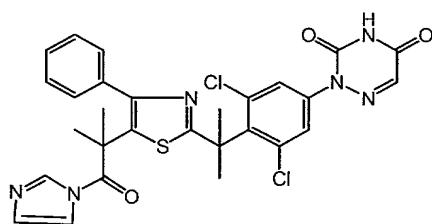


b) A mixture of intermediate (8) (0.05 mol) and intermediate (35) (0.05 mol) in ethanol (150 ml) and DMF (50 ml) was stirred for 72 hours at 70°C. The reaction product was poured out into water and then separated into its layers. The aqueous layer was extracted with ethyl acetate. The combined organic layer was washed with water, dried, filtered and the solvent was evaporated under reduced pressure. The residue was crystallized from acetonitrile. The precipitate was filtered off and dried, yielding



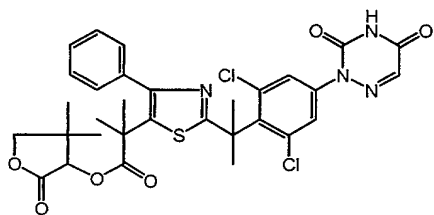
c) A mixture of intermediate (36) (0.00275 mol) and 1,1'-carbonylbis-1*H*-imidazole (0.00416 mol) in dichloromethane (30 ml) was stirred at room temperature for 2 hours. Butyric acid (0.00416 mol) was added at room temperature. The mixture was stirred at room temperature overnight. The solvent was evaporated under reduced pressure. The residue was purified by column chromatography over silica gel (eluent: CH₂Cl₂/THF 100/0 to 80/20). The pure fractions were collected and the solvent was evaporated. The residue was stirred in ethyl acetate/hexane 30/70). The precipitate was filtered off and

dried, yielding 0.8g of



(intermediate 37).

d) Intermediate (37) (0.00173 mol) and dihydro-3-hydroxy-4,4-dimethyl-2(3*H*)-furanone (0.04 mol) were stirred at 100°C for 2.5 hours. The mixture was poured out into water and then extracted with ethyl acetate. The organic layer was separated, dried, filtered and the solvent was evaporated. The residue was purified over silica gel on a glass filter (eluent: CH₂Cl₂/THF 100/0 to 98/2). The pure fractions were collected and the solvent was evaporated. The residue was stirred in ethyl acetate/hexane (1/1). The precipitate was filtered off and dried at 50°C overnight, yielding 0.38g of



(compound 147).